The American Journal of Medicine

July 1952

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Editorial

Disorders of the Blood in Disseminated Lupus Erythematosus. C. LOCKARD CONLEY 1

Clinical Studies

Thrombotic Thrombocytopenic Purpura
BENJAMIN R. GENDEL, JOSEPH M. YOUNG AND ALFRED P. KRAUS 3

These two cases and the accompanying discussion relate to an intriguing disorder which still presents many problems in classification, etiology and management. As is brought out, although a discrete entity, the relationship to allergic vascular reactions and to certain aspects of disseminated lupus erythematosus remains obscure.

Hemostatic Defect in Thrombocytopenia as Studied by the Use of ACTH and Cortisone. . WILLIAM W. FALOON, RICHARD W. GREENE AND EUGENE L. LOZNER 12

Decreased platelets and abnormal vascular fragility characterize the purpuras due both to primary and secondary thrombocytopenia. The present study attempts to make use of the effects of ACTH and cortisone to distinguish the factors responsible for these abnormalities. Interesting results were obtained, suggesting that abnormal platelet production and vascular resistance are due to distinct hormonal agents.

Effect of Corticotropin (ACTH) and Cortisone on Idiopathic Thrombocytopenic Purpura . . . . . SLOAN J. WILSON AND GUSTAVE EISEMANN 21

The effects of ACTH and cortisone in idiopathic thrombocytopenic purpura are of both practical and theoretic interest. In this series five of twelve patients showed at least temporary response to these agents.

Hypercoagulability of the Blood of Patients with Hepatic Cirrhosis Following Administration of ACTH
WILLIAM J. EISENMENGER, ROBERT J. SLATER AND ALFRED M. BONGIOVANNI 27

That ACTH administration may cause hypercoagulability of the blood is confirmed in this study, in which this phenomenon was found to occur even in cirrhotics with deficiencies in plasma prothrombin, fibrinogen and platelets. It is not known what agency is responsible, nor did this painstaking investigation throw any light on the coagulation mechanism affected. Of practical concern

Contents continued on page 5

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1. Pelner, L., and Waldman, S.: Postgrad. Med. *11*:49 (Jan.) 1952.
2. Pelner, L., and Waldman, S.: Am. Pract. *3*:293 (Apr.) 1952.

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is the development of thromboembolism; in three patients in this series portal thrombosis developed while the patients were receiving ACTH.

Chronic Hypoplastic Neutropenia . THEODORE H. SPAET AND WILLIAM DAMESHEK 35

The authors have collected four cases of severe neutropenia of many years' duration, associated with marked hypoplasia of granulocytic precursors as the only abnormality in the bone marrow. These patients exhibited slight to moderate splenic enlargement but did not respond to splenectomy, thus excluding primary splenic neutropenia. It is suggested that these cases represent a more or less distinct syndrome for which the term "primary hypoplastic neutropenia" is suggested.

Mediterranean Hemopathic Syndromes (Cooley's Anemia) in Adults. Study of a Family with Unusual Complications
HAROLD W. MARCH, SAMUEL M. SCHLYEN AND SAMUEL E. SCHWARTZ 46

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Circulating Blood Eosinophils in Acute Infectious Disease and Eosinopenic Response
H. A. WEINER AND DIMITRY MORKOVIN 58

Resurgent interest in the eosinophil and eosinopenia makes this review timely. The authors point out that the eosinopenia quite regularly occurring in severe and acute infections probably is related to the alarm reaction as defined by Selye. They draw some provocative conclusions on this basis.

Seminars on Gastrointestinal Physiology

A Physiologic and Clinical Consideration of the Pressures Developed in the Digestive Tract . . . . . J. P. QUIGLEY AND DANIEL A. BRODY 73

Drs. Quigley and Brody introduce the seminars on gastrointestinal physiology with an account of the recent improvements in technics for registering intraluminal pressures in the several sectors of the gastrointestinal tract. Normal values are given, also pressure levels after vagotomy and in patients with peptic ulcer and gastritis.

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Hemorrhagic State during Pregnancy. With the Presence of Maternal Rh Antibodies, Death of the Fetus and Hypofibrinogenemia

OSCAR D. RATNOFF, CARL F. LAUSTER, JOHN G. SHOLL AND MYRON O. SCHILLING 111

The case described by the authors presented an interesting problem in hemorrhaging tendency which turned out to be related to hypofibrinogenemia, the cause of which could not be ascertained definitely. The hemorrhagic state was corrected by subtotal hysterectomy, one of the puzzling features of the case.

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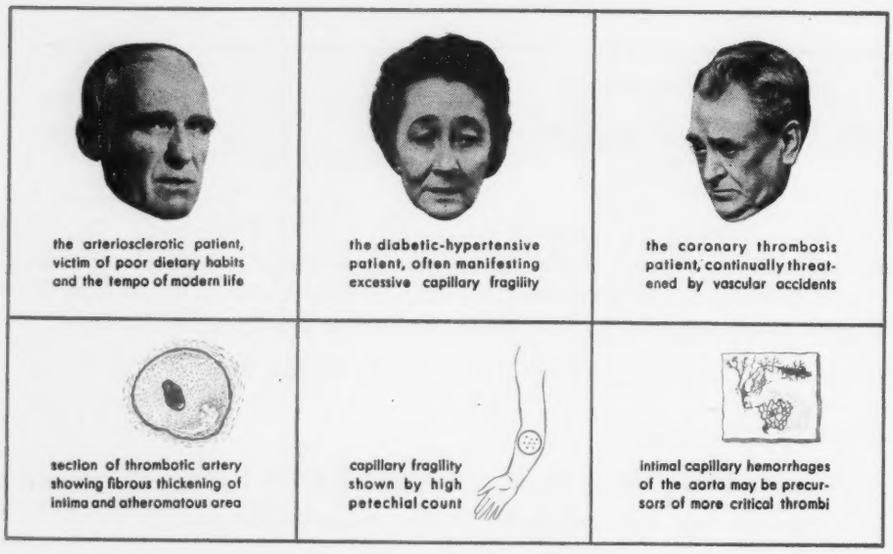

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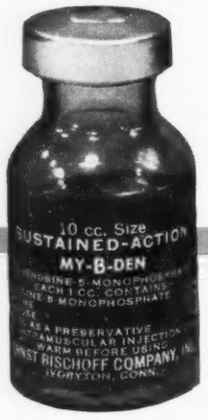

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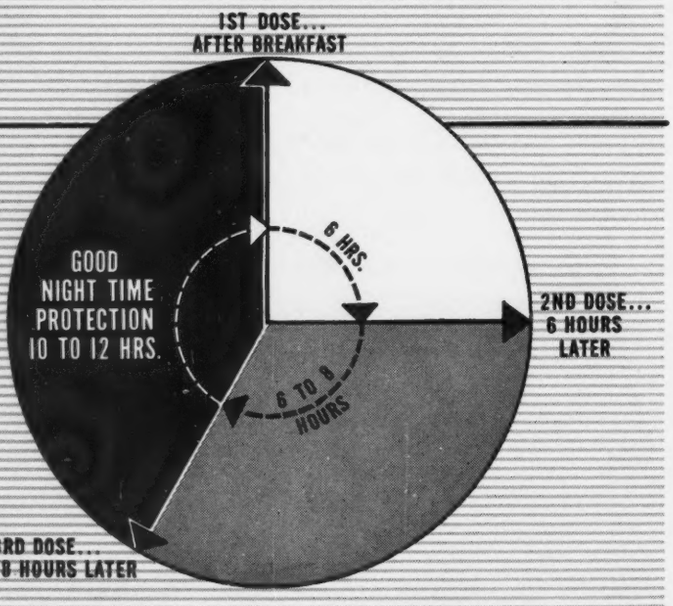

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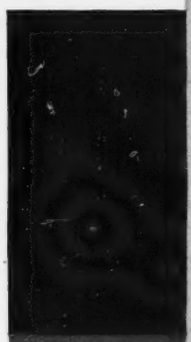

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1. Behrman, H. T., Combes, F. C., Bobroff, A., Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
2. Turell, R.: New York St. J.M. 50:2282, 1950.
3. Heimer, C. B., Grayzel, H. G., and Kramer B.: Archives Pediat. 68:382, 1951.

SCURVY

is more common than many think

AGE	NO. SUBJECTS EXAMINED	NO. WITH SCURVY	% WITH SCURVY	NO. WHITE SUBJECTS	NO. WITH SCURVY	NO. NEGRO SUBJECTS	NO. WITH SCURVY
0–15 da.	360	0	0	174	0	186	0
16–30 da.	90	1	—	41	1	49	0
1 mo.	99	0	0	48	0	51	0
2 mo.	90	2	2.2	34	2	56	0
3 mo.	69	3	4.3	31	3	38	0
4 mo.	79	2	2.5	26	1	53	1
5 mo.	73	12	16.5	25	3	48	9
6 mo.	53	13	24.5	19	5	34	8
7 mo.	54	10	18.5	22	7	32	3
8 mo.	40	5	12.5	18	2	22	3
9 mo.	38	10	26.3	12	4	26	6
10 mo.	41	5	12.2	16	0	25	5
11 mo.	40	3	7.5	12	0	28	3
12–23 mo.	177	3	—	68	1	109	2
Total.....	1303	69		546	29	757	40

PREVALENCE OF SCURVY

Histological examination* of bone structure in 1300 infant post mortems revealed that scurvy occurred more than 10 times as frequently as is usually shown by clinical diagnosis. The most susceptible age is from the fifth through the eleventh month, with approximately 17% of infants exhibiting the histological signs. Over half of the children with scurvy had never received supplemental vitamin C. How easy to prevent, when Florida citrus is so rich in vitamin C content — so convenient, so economical, and so pleasant to take!

* *Bull. Johns Hopkins Hosp. 87:569, 1950.*

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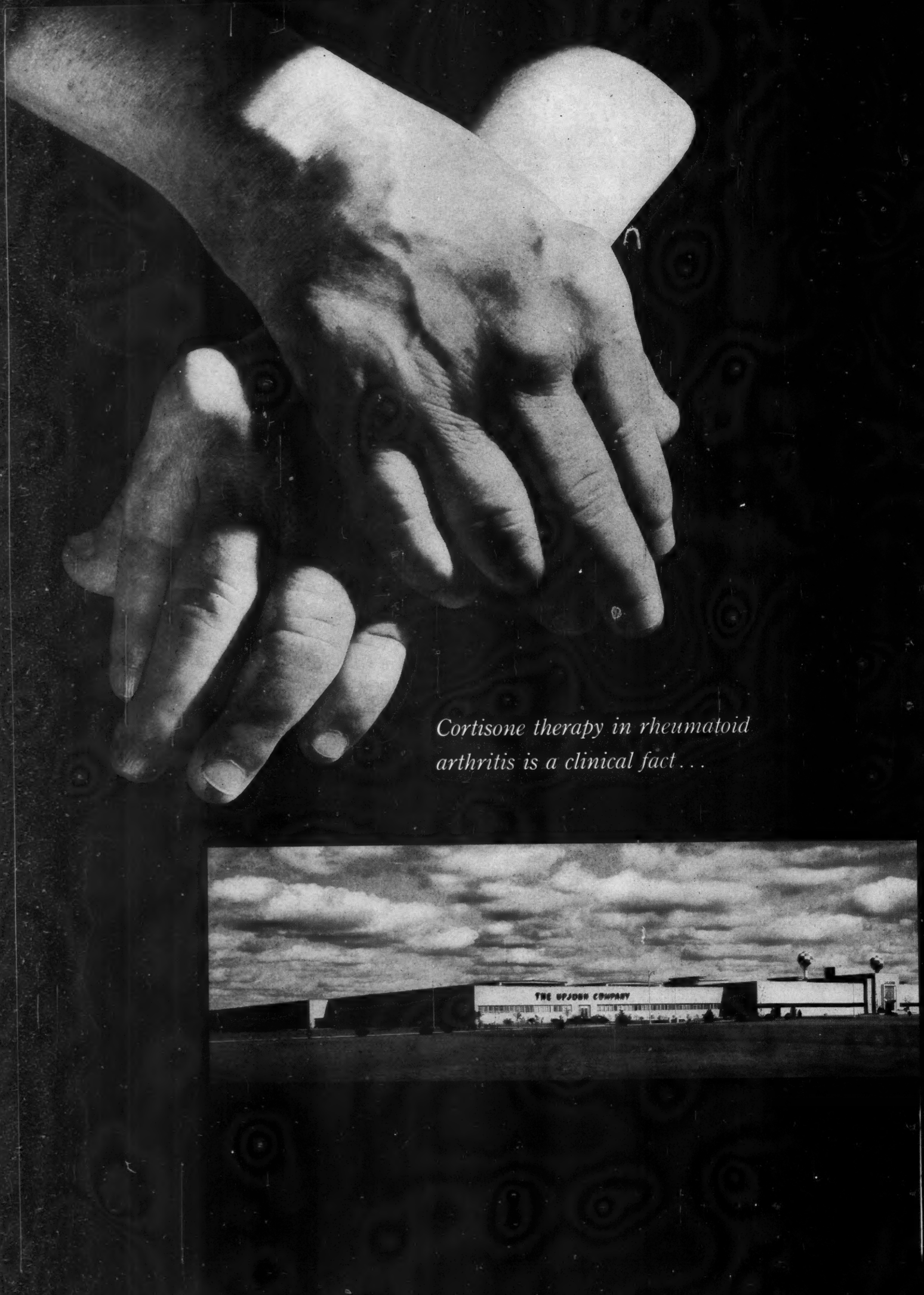

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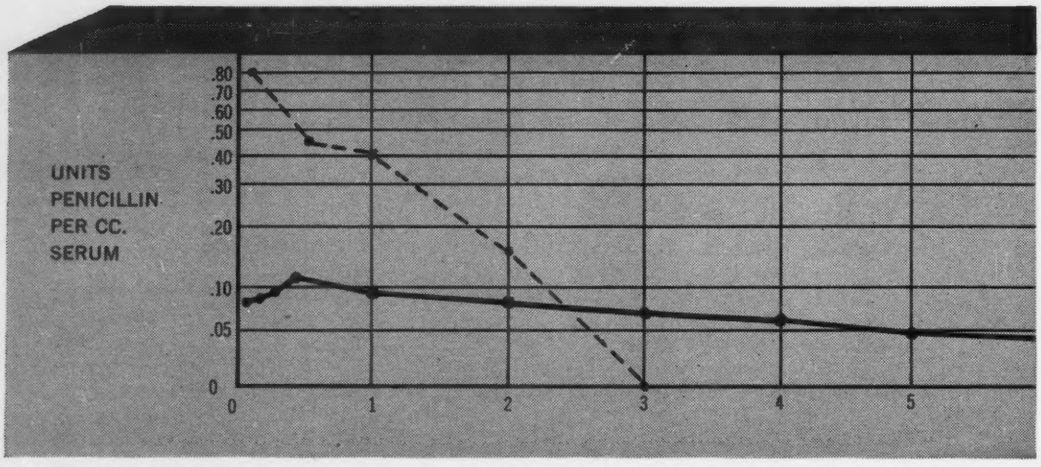

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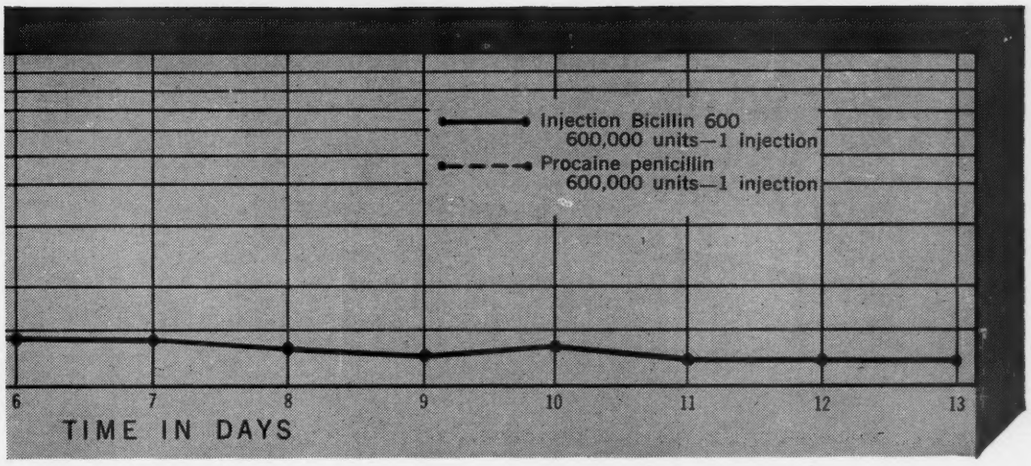

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**Herpes Zoster: Its treatment with Protamide. Frank C. Combes, M. D., and Orlando Canizares, M. D., New York State Journal of Medicine (March) 1952.*

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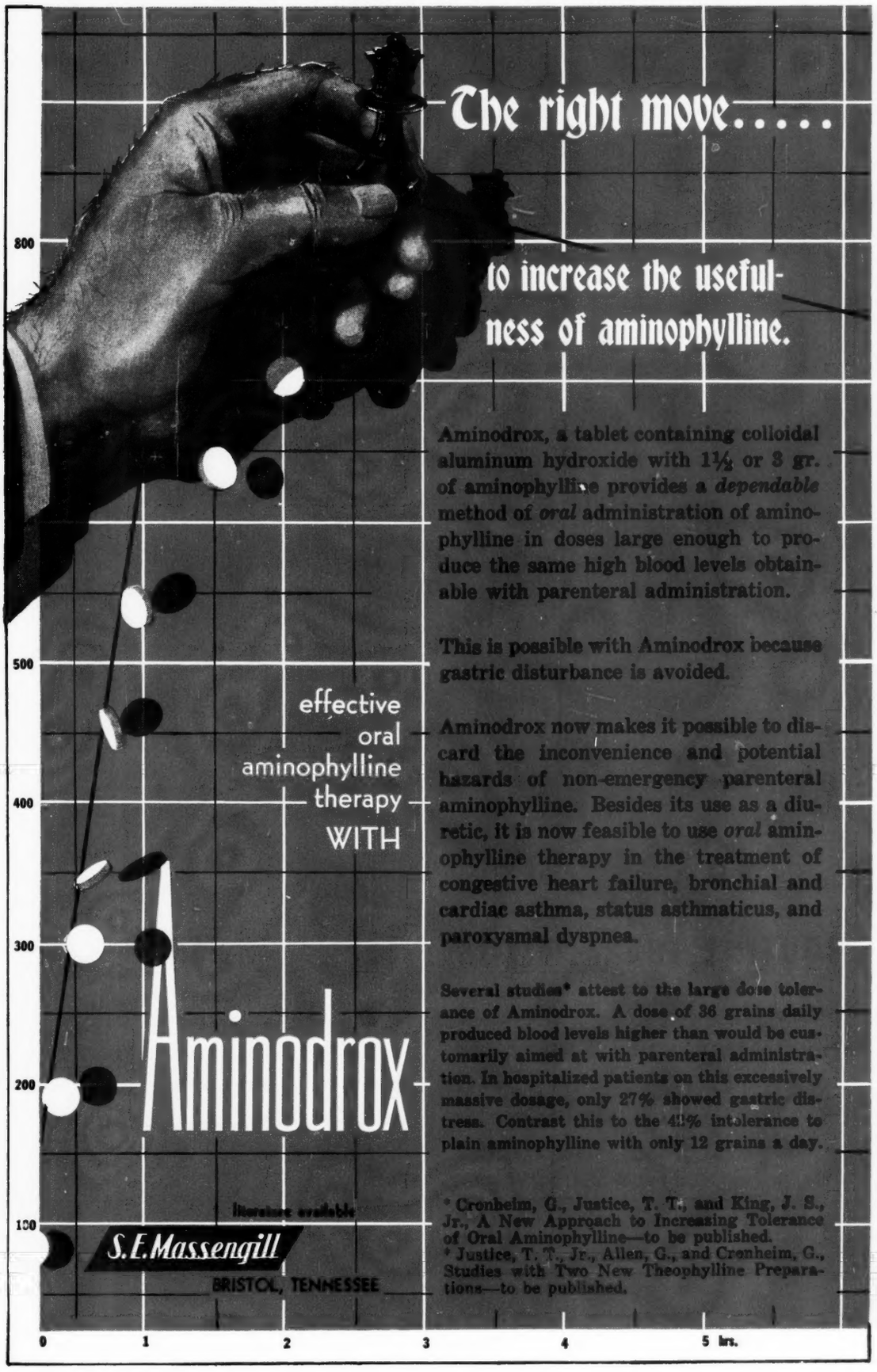

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BRISTOL, TENNESSEE

* Cronheim, G., Justice, T. T., and King, J. S., Jr., A New Approach to Increasing Tolerance of Oral Aminophylline—to be published.
† Justice, T. T., Jr., Allen, G., and Cronheim, G., Studies with Two New Theophylline Preparations—to be published.

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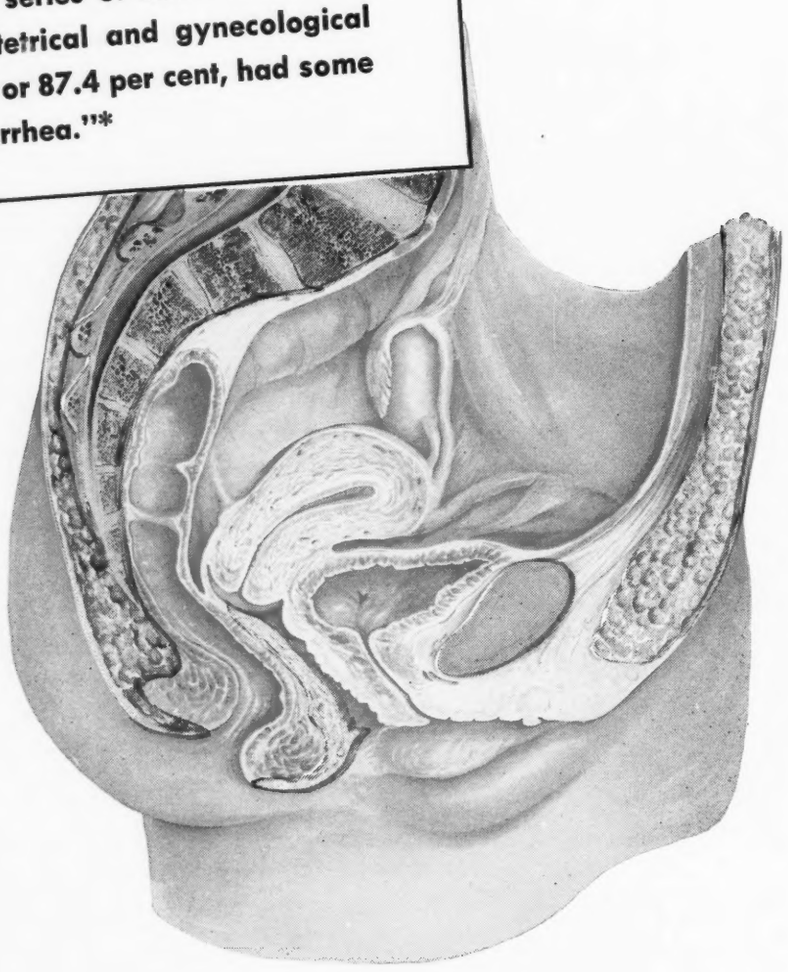

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*Collins, J. H., and Ellington, C. J., Jr.: Vulvovaginitis, New Orleans M. & S. J. *104*:220 (Dec.) 1951.

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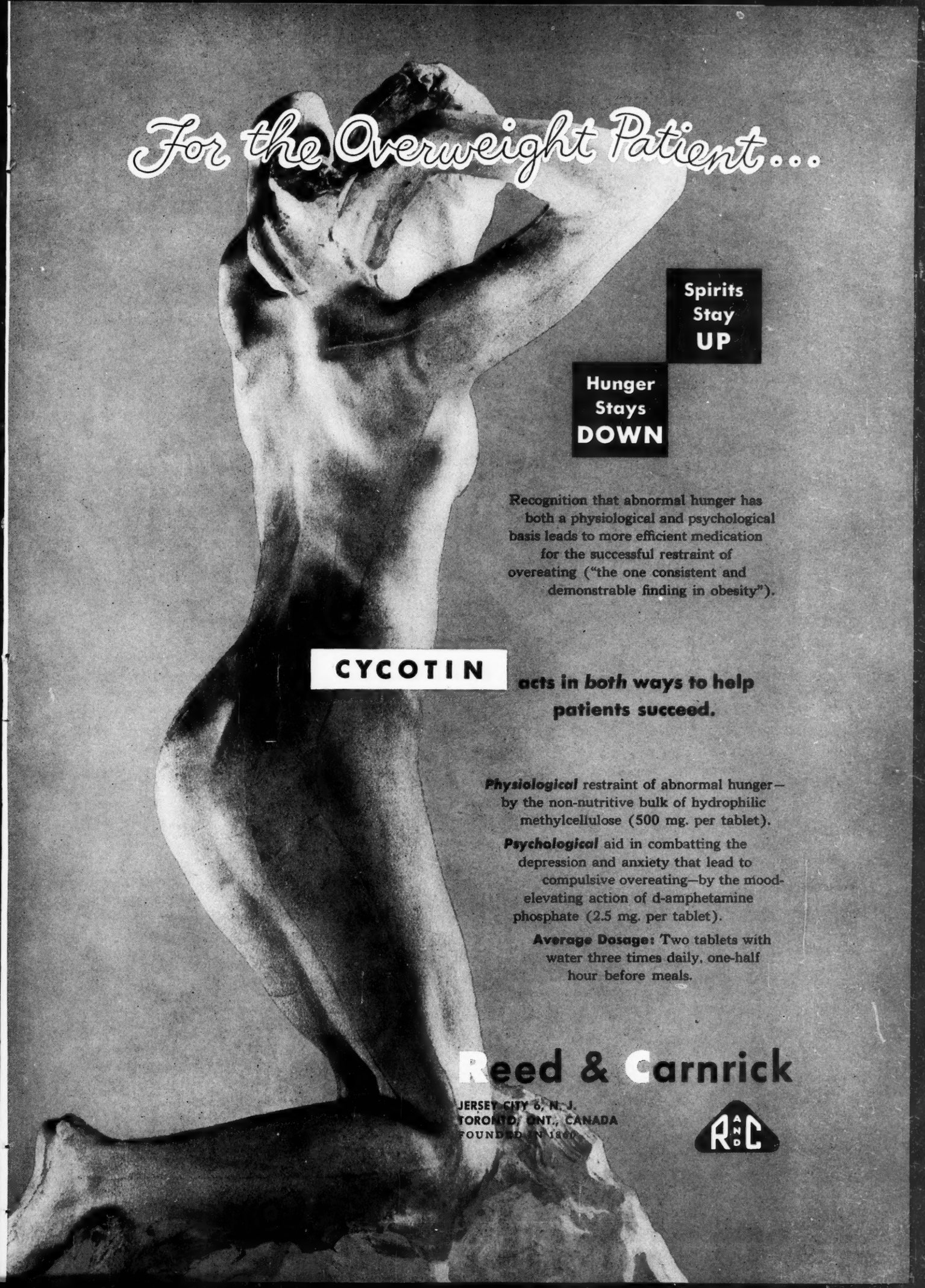
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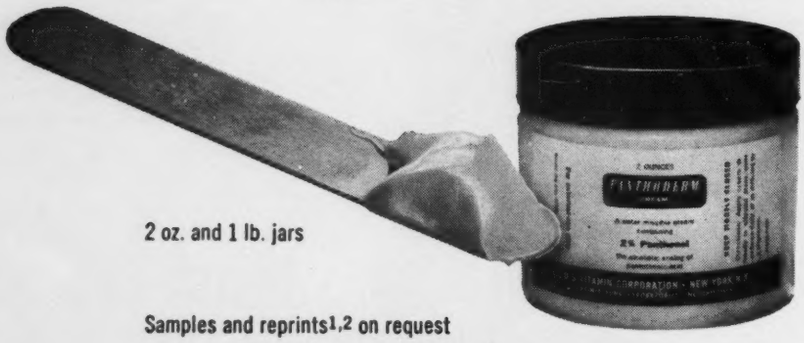

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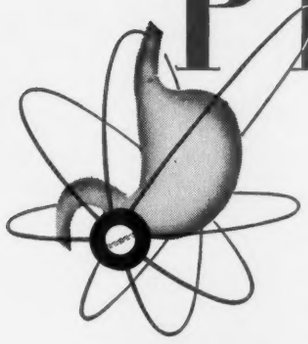

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The American Journal of Medicine

VOL. XIII JULY, 1952 No. 1

Editorial

Disorders of the Blood in Disseminated Lupus Erythematosus

THE increasingly frequent recognition of disseminated lupus erythematosus is providing an opportunity for physicians to become familiar with some of the unusual syndromes by which this disease may be manifested. The discovery of the L.E. cell[1] introduced a valuable diagnostic aid, and subsequent observations have shown that the L.E. cell phenomenon is highly specific, occurring rarely if at all in other conditions.[2–4] In most cases of disseminated lupus, L.E. cells can be demonstrated in films of the buffy coat of peripheral blood. Nevertheless, in some typical instances of the disease the peculiar cells cannot be found on repeated examination of blood and bone marrow. At the Johns Hopkins Hospital the blood of a heterogeneous group of more than 700 patients has been examined for L.E. cells. These cells have been identified in thirty-seven cases in all of which the clinical features were compatible with the diagnosis of disseminated lupus. When L.E. cells are demonstrable, they usually persist over a period of months or years. During the administration of ACTH or cortisone the number of L.E. cells may decrease but they rarely disappear. Typical L.E. cells may be readily demonstrated in some cases of asymptomatic lupus, while they may not be found in occasional cases of the fulminating disease. Thus there seems to be no regular correlation between degree of activity of the disease process and the finding of the apparently pathognomonic cells.

Certain abnormalities of the formed elements of the blood are rather common in disseminated lupus. Michael and his associates[5] have recently reviewed in detail the results of blood examinations of a large group of patients with this disease. Anemia is frequently encountered and leukopenia and thrombocytopenia are not uncommon. In occasional cases of lupus a disorder of the blood may be the outstanding clinical feature, and in these instances the disease may simulate a primary blood dyscrasia. Thrombocytopenic purpura, indistinguishable from "idiopathic" purpura, is not rarely an early manifestation of disseminated lupus.[5–7] In these cases there may or may not be a history of joint pain, pleuritic pain or other suggestive evidence of lupus. Often the thrombocytopenia is not accompanied with anemia or leukopenia but L.E. cells may be demonstrated in the blood. Smears of aspirated bone marrow contain many megakaryocytes, and the marrow pattern cannot be distinguished from that seen in "idiopathic" thrombocytopenic purpura. The spleen often is not palpable but microscopic examination of the spleen may show the characteristic periarterial fibrosis. Splenectomy has been followed by a prompt and persistent rise in the platelet count

[1] HARGRAVES, M. M., RICHMOND, H. and MORTON, R. Presentation of two bone marrow elements: the "tart" cell and the "L.E." cell. *Proc. Staff Meet., Mayo Clin.*, 23: 25–28, 1948.

[2] HASERICK, J. R. Plasma L.E. test in systemic lupus erythematosus. *J. A. M. A.*, 146: 16–20, 1951.

[3] SUKSTA, A. and CONLEY, C. L. Some observations on the L.E. cell. *J. Lab. & Clin. Med.*, 37: 597–602, 1951.

[4] LEE, S. L., MICHAEL, S. R. and VURAL, I. L. The L.E. (lupus erythematosus) cell. *Am. J. Med.*, 10: 446–451, 1951.

[5] MICHAEL, S. R., VURAL, I. L., BASSEN, F. A. and SCHAEFER, L. The hematologic aspects of disseminated (systemic) lupus erythematosus. *Blood*, 6: 1059–1072, 1951.

[6] LYON, J. M. Acute lupus erythematosus. *Am. J. Dis. Child.*, 45: 572–583, 1933.

[7] TUMULTY, P. A. and HARVEY, A. M. The clinical course of disseminated lupus erythematosus. An evaluation of Osler's contributions. *Bull. Johns Hopkins Hosp.*, 85: 47–73, 1949.

in most of the patients studied, but other manifestations of lupus have eventually appeared.

Hemolytic anemia may occur in patients with disseminated lupus.[5,8] The anemia may appear at a time when other evidences of lupus are mild or absent. The hemolytic process is often associated with the presence of autoantibody in the serum and the Coombs' test may be positive. It is of interest that the Coombs' test is sometimes positive in cases of lupus in which increased blood destruction is not evident.[9] Prolonged therapy with ACTH and splenectomy have been observed to have no effect on the autoantibody titer, although the anemia may improve. There appears to be no good evidence to support the hypothesis that the blood abnormalities in lupus can be attributed to "hypersplenism." In one patient studied at the Johns Hopkins Hospital hemolytic anemia first appeared two years after splenectomy had been performed for thrombocytopenic purpura.

A rare form of hemorrhagic disorder has been recognized to be a manifestation of lupus. Two patients examined at the Johns Hopkins Hospital were found to have a circulating anticoagulant which retarded the conversion of prothrombin to thrombin, even in the presence of tissue extract thromboplastin. These patients apparently had in their serum an abnormal protein which interfered with the normal clotting mechanism. Other cases of atypical hemorrhagic disorders have been reported in which the clinical descriptions and autopsy findings suggest the possibility of lupus.[10] Recent observations have indicated that there may be a relationship between "thrombotic thrombocytopenic purpura" and disseminated lupus but L.E. cells have not been demonstrated in the blood of patients with this disease.[11]

Hematologists are often unable to provide an etiologic explanation for the conditions which they are called upon to treat. The term "idiopathic" has necessarily been overused in this branch of medicine. It is a step forward, therefore, to discover that some previously obscure disorders can now be satisfactorily classified.

C. Lockard Conley, M.D.
Johns Hopkins Hospital,
Baltimore, Md.

[8] Dubois, E. L. Acquired hemolytic anemia as the presenting syndrome of lupus erythematosus disseminatus. *Am. J. Med.*, 12: 197–203, 1952.

[9] Evans, R. S., Takahashi, K., Duane, R. T., Layne, R. and Liu, C. K. Primary thrombocytopenic purpura and acquired hemolytic anemia: evidence for a common etiology. *Arch. Int. Med.*, 87: 48–65, 1951.

[10] Ley, A. B., Reader, G. G., Sorenson, C. W. and Overman, R. S. Idiopathic hypoprothrombinemia associated with hemorrhagic diathesis, and the effect of vitamin K. *Blood*, 6: 740–755, 1951.

[11] Barondess, J. A. Thrombotic thrombocytopenic purpura. *Am. J. Med.* In press.

Clinical Studies

Thrombotic Thrombocytopenic Purpura*

BENJAMIN R. GENDEL, M.D., JOSEPH M. YOUNG, M.D. *and* ALFRED P. KRAUS, M.D.
Memphis, Tennessee

DURING the past five years a number of patients who presented a fulminating thrombocytopenic purpura have been reported. These cases have been separated from the group of idiopathic thrombocytopenic purpuras by virtue of characteristic clinical and histopathologic features. Although the first case was reported in 1925 by Moschcowitz,[1] the syndrome was not clearly defined until 1936 when Baehr and his co-workers[2] reported four cases. In 1947 two groups of workers[3,4] reviewed the subject and Singer[4] suggested the name of thrombotic thrombocytopenic purpura. The disease is characterized by the clinical triad of hemolytic anemia, thrombocytopenic purpura and involvement of the central nervous system. Histologically, there are generalized hyaline arteriolar and capillary lesions which have been considered to be platelet thromboses. Although the disease has been considered rare, there are now thirty-two reported cases in the literature.

The clinical and pathologic findings in two additional cases are presented in this report along with a brief review of this interesting disease.

CASE REPORTS

CASE I. The patient was a thirty year old white man who had thrombophlebitis of his left leg in 1942. This was followed by refractory leg ulcers which did not heal completely despite various types of treatment. There were recurrent episodes of thrombophlebitis of both lower extremities and several bilateral venous ligations were performed. Subsequently, ulcers developed on the right leg. In April, 1949, the patient was found to be anemic with an erythrocyte count of 2.6 million. In addition the chest x-ray showed haziness of the left lower lung field. In July, 1949, an episode of fever, urinary frequency and pain in the costovertebral angles occurred. Albuminuria, hematuria and pyuria were found. Following treatment with aureomycin and several blood transfusions the fever subsided. During his illness an erythematous eruption appeared over the cheeks and bridge of the nose and he also developed raised, purplish skin lesions on the neck. The fever and rash disappeared but the leg ulcers persisted and he was admitted to this hospital on October 1, 1949.

The patient was a well developed, fairly well nourished white man who appeared chronically ill. The blood pressure was 130/85. The heart and lungs were normal. Liver, spleen and kidneys were not palpable. The right dorsalis pedis and posterior tibial pulses were faint. The left dorsalis pedis pulsation was normal but the posterior tibial was diminished. There was a scar of a high venous ligation on the left and several bilateral low ligation scars. There were several scars of healed ulcers and a number of open ulcers of both lower extremities.

On admission the erythrocyte count was 2.8 million; hemoglobin, 8.2 gm.; leukocyte count, 5,800 with 56 per cent neutrophils, 39 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils. The platelet count was 392,000. The initial urine showed a specific gravity of 1.015 and 1+ albumin. There were no abnormal elements in the urinary sediment. The serum proteins were 7.5 gm. per cent with 3.4 gm. of albumin and 4.1 gm. of globulin. Prothrombin time was 100 per cent. Serologic tests for syphilis were positive in low titer. Bleeding and coagulation times were normal. The blood count four days later was approximately the same; the platelet count was 715,000; reticulocytes, 3.4 per cent and hematocrit, 23 per cent. Bone marrow was normal. The red cell hypotonic saline fragility test was nor-

* From the General Medicine and Hematology Section of the Medical Service and the Laboratory Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tenn. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion and policy of the Veterans Administration.

mal. Gastric analysis showed free hydrochloric acid after histamine. Sickle cell preparation was negative. The coagulation time twelve days after admission was moderately prolonged, nineteen, twenty-nine and thirty-five minutes in each of three tubes; bleeding time was normal. A protamine-heparin titration test showed the control end point to be 0.14 cc. of protamine sulfate. The patient's blood did not clot at all, indicating the presence of a heparin-like anticoagulant. Spinal fluid examination was normal. A urea clearance test showed a blood urea nitrogen of 18 mg. per cent and a clearance of 62 per cent of average normal function.

During hospitalization the urine contained traces of albumin with no abnormalities in the sediment. Two cultures of sputum for acid-fast bacilli were negative. Liver function tests showed no BSP retention in forty-five minutes; cephalin flocculation, 3+ in forty-eight hours; total serum bilirubin, 0.9, and one minute, 0.07 mg. per cent. Studies of the blood for iso- and auto-agglutinins and hemolysins showed a cold iso- and auto-agglutinin with a titer of 1:4. The urinary urobilinogen was 9.5 mg. per day; the fecal urobilinogen, 300 mg. per day. The latter was considered elevated because of the anemia which was present and the results were considered consistent with a hemolytic anemia. Repeated studies of the blood showed a slight reticulocytosis with counts of 2.0 to 3.8 per cent and normal platelets. The last blood study on November 18, 1949, two days before the patient's death, showed an erythrocyte count of 2.32 million; hemoglobin, 6.6 grams; leukocyte count, 6,600 with a normal differential; platelet count, 289,000 (normal in our laboratory, 400,000 to 800,000); hematocrit, 21 per cent; reticulocytes, 1.8 per cent. Terminally the patient developed azotemia with serum nonprotein nitrogen levels up to 68 mg. per cent. Six blood cultures were sterile.

The patient was afebrile on admission and was studied to determine the cause of his leg ulcers and anemia. Low-titered positive serologic tests for syphilis were found although there was no history of syphilis and the spinal fluid was normal. With the realization that the patient's positive test might be a biologic false positive reaction, it was decided to treat him with penicillin starting on October 10, 1949. Two days later he developed a mild penicillin reaction consisting of edema of the right periorbital region. Benadryl® was given and the swelling subsided. The patient was able to complete a course of six million units of penicillin but without any benefit. On October 26, 1949, the patient was awakened by a paroxysmal tachycardia which was shown by electrocardiogram to be auricular tachycardia. This was controlled by quinidine. About this time slight fusiform swelling and stiffness of the fingers appeared and he could not clench his fists. The temperature rose and remained between 101° and 102°F. until his death. He developed pain in the toes of the right foot and these became cyanotic and cold with manifestations of Raynaud's phenomenon. A butterfly rash appeared over the bridge of the nose and cheeks. It was the opinion of the consulting dermatologists that this was a seborrheic dermatitis and the rash subsided under treatment with ammoniated mercury ointment. In an effort to control the febrile downhill course, penicillin treatment was re-instituted on November 5, 1949. In spite of concomitant administration of benadryl, another allergic response consisting of ecchymotic urticarial lesions occurred. The erythrocyte count fell to 2.3 million and was not improved by two 500 cc. blood transfusions. The leg ulcers had gradually healed during the course of hospitalization.

Because of the unfavorable course with fever and evidence of multiple system involvement including pneumonitis, arthritis, butterfly rash, albuminuria, anemia and leukopenia, hyperglobulinemia and low-titered positive serologic tests for syphilis, a diagnosis of disseminated lupus erythematosus was made. However, two preparations for "L.E. cells" were negative. The Raynaud's phenomenon progressed to gangrene of the right great toe. A right lumbar paravertebral block with metycaine® was done on November 17, 1949, and afforded temporary relief of pain in the toe. On November 18, 1949, the patient developed a tremor of the left hand and lumbar pain. He became very apprehensive and gradually lapsed into coma. The blood pressure fell to 98/50. He was placed in an oxygen tent and later became oriented. However, the improvement was transient and the patient developed peripheral vascular collapse and died on November 20, 1949, seven weeks after admission.

Autopsy examination showed scarring of both lower extremities. The pleural cavities were obliterated by fibrous adhesions. The lungs were markedly edematous and congested. The heart

FIG. 1. Case I. Heart showing verrucous lesions along margin of mitral valve.

weighed 500 gm. and when opened showed verrucous nodules along the margins of the mitral leaflets. (Fig. 1.) The aorta was not remarkable. There was a hemorrhagic area which narrowed the lumen of the right hypogastric artery. The spleen weighed 690 gm. and the liver 2,500 gm. The adrenals showed extensive hemorrhages involving both the cortex and medulla. The kidneys weighed 250 gm. each. Their capsules stripped with ease, and on section there was poor corticomedullary demarcation.

Microscopic examination disclosed widely disseminated lesions of the capillaries and arterioles. These consisted of hyaline masses plugging the lumina of these vessels. (Fig. 2.) The plugs frequently were covered by endothelium and were continuous with the vessel wall. Other vessels were markedly dilated and thin-walled and much of the structure of the wall was absent. These changes were found in the heart, liver, spleen, pancreas, adrenals, kidneys and brain. A fine interstitial fibrosis most marked near the involved vessels was observed in the heart. There was slight hypertrophy of some muscle fibers and others showed degenerative changes. There was moderate perivascular fibrosis. The verrucous lesions of the mitral valve were made up of fibroblasts and strands of fibrinoid material. Around the involved vessels in the pancreas there were small areas of recent necrosis. The adrenals were almost completely necrotic with a surrounding zone of hemorrhage and inflammatory reaction. The bone marrow showed an increase in megakaryocytes. The section from the hypogastric artery showed hemorrhage in the wall and a few thrombosed adventitial vessels. A section from pectoral muscle was normal. The final anatomic diagnoses were: (1) thrombotic thrombocytopenic purpura with generalized small vessel thrombi; (2) adrenal necrosis, bilateral; (3) pulmonary edema and congestion of spleen, liver and kidneys; (4) scarring of legs.

CASE II. This patient was a thirty-one year old white man who was admitted to this hospital on February 22, 1951, because of malaise accompanied by low back pain, nocturia, urinary frequency and urgency of one week's duration. He consulted his local physician who told him that his blood count was low. He was given an injection of penicillin and eight hours later developed urticaria and swelling of the face, arms and hands. This reaction subsided in about two days. Four days prior to admission the patient became nauseated and vomited several

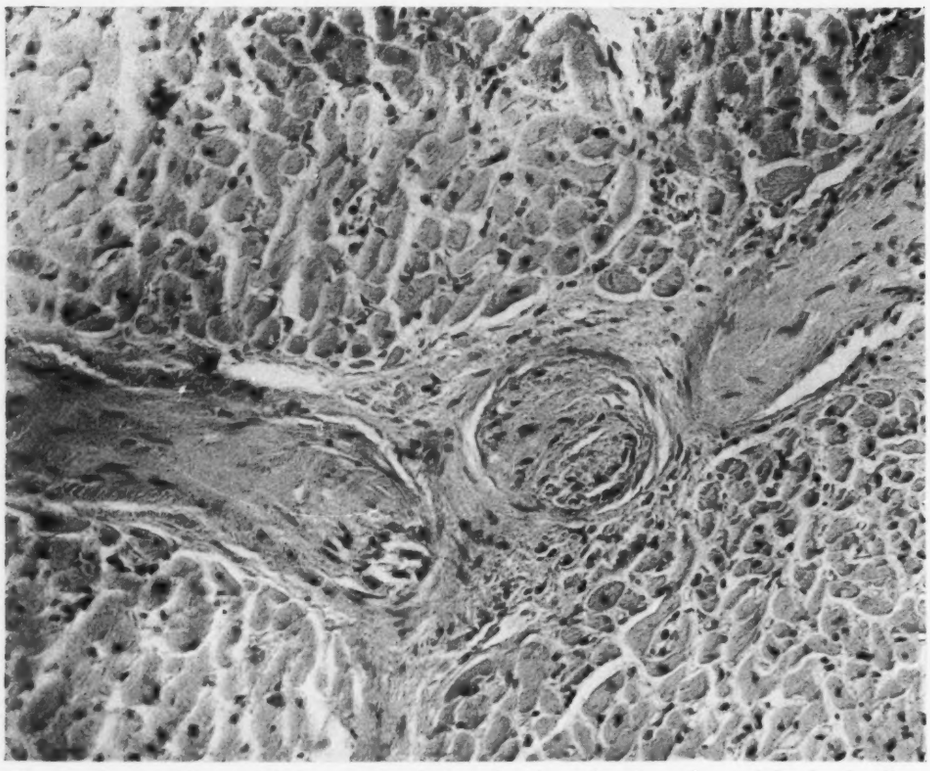

FIG. 2. Case 1. Characteristic vascular lesion showing plugging of arterioles by hyaline material; hematoxylin and eosin × 200.

times. Headache developed and there was increasing malaise. Small subconjunctival hemorrhages occurred. Two or three days before admission the urine became deep orange in color. On the day before admission the patient became aware of a low-grade fever. Accompanying these symptoms there were marked anorexia and weight loss.

Two and a half years previously the patient had an illness characterized by malaise, low-grade fever, swelling of the feet, nocturia, frequency and dark urine. He was told he had "kidney trouble" and the symptoms subsided in two or three months although the urinary symptoms recurred at intervals. His last attack was six or eight months prior to admission; he was cystoscoped but the findings were unknown.

Physical examination showed a well developed, obese, white male who did not appear acutely ill. The temperature was 99°F. and the blood pressure 130/90. Bilateral subconjunctival hemorrhages and slight icterus were present. There were no retinal changes. There was a grade two systolic murmur at the apex but no other cardiac abnormalities. The liver, spleen and kidneys were not palpable. There was slight tenderness in the right costovertebral angle. Scattered petechiae were present over the extremities.

On admission the erythrocyte count was 2.8 million, with 7.8 gm. of hemoglobin. The leukocyte count was 13,250 with 80 per cent neutrophils and 20 per cent lymphocytes. The platelet count was 201,600. Bleeding and coagulation times were normal on admission. The urine showed albuminuria with several erythrocytes, leukocytes and granular casts in the sediment. The serum non-protein nitrogen was 49 mg. per cent on admission. The level remained the same until March 8, 1951, when it rose to 112 mg. per cent. The total serum bilirubin was 1.6 mg. per cent, and the one-minute fraction was 0.1 mg. per cent. The prothrombin time was 100 per cent; total cholesterol, 500 mg. per cent and esters 320 mg. per cent. Urinary urobilinogen varied from 1.3 to 3.4 mg. per day. Studies of fecal urobilinogen could not be completed. Other tests of liver function including proteins, cephalin flocculation and thymol turbidity were normal. On March 5, 1951, the total blood cholesterol was still elevated to 390 mg. and esters to 260 mg. per cent. The direct Coombs test was negative on two occasions. No auto- or iso-hemolysins or agglutinins

were found. A blood culture was sterile. Serologic tests for syphilis were negative.

The course in the hospital was characterized by a low-grade fever up to 100°F. during the first week. The patient was originally thought to have an acute exacerbation of chronic nephritis with secondary anemia. Two days after admission the patient suddenly developed transient aphasia and right facial weakness, which lasted about an hour. Several blood transfusions were given without influencing the blood count. On February 28, 1951, he developed a transient *left* facial weakness with mental confusion and aphasia, all of which disappeared in about an hour. Blood count at this time showed an erythrocyte count of 2.43 million with 6.8 gm. per cent of hemoglobin; leukocytes, 10,200 with a differential of 3 myelocytes, 8 metamyelocytes, 15 band cells, 47 segmented neutrophils, 18 lymphocytes, 8 monocytes and 1 eosinophil. There were 9 nucleated erythrocytes per 100 leukocytes. The hematocrit was 22 per cent and there were 21.8 per cent reticulocytes. Platelets were 29,160. Because of the typical blood findings and the presence of transient, bizarre neurologic findings a diagnosis of thrombotic thrombocytopenic purpura was made. The tip of the spleen was palpable at that time. The patient had two other episodes of transient facial palsy and these were followed by an episode of restlessness, disorientation, stupor and right hemiplegia. The temperature rose to 103.4°F. and on March 6, 1951, treatment was started with aureomycin and ACTH, 25 mg. every six hours. Several additional blood transfusions were administered. The hemiplegia lasted only twenty-four hours, and on the following day the patient became more responsive although aphasia was present. Fever continued despite treatment with aureomycin and ACTH. The patient again lapsed into stupor and died on March 12, 1951, eighteen days after admission, about four weeks after the onset of his illness. He received a total of 625 mg. of ACTH.

At autopsy there were scattered petechial hemorrhages and ecchymoses over the extremities. The pericardial sac contained 200 cc. of a brownish cloudy fluid and the epicardial surfaces showed numerous petechiae. The lungs were edematous. The heart weighed 420 gm. and showed many small areas of hemorrhage throughout the muscle. The liver weighed 3,000 gm. and the spleen, 300 gm. The kidneys were tense and had a combined weight of 410 gm.; the capsule stripped with ease. There were numerous petechiae in the cortex and to a lesser extent in the medulla. The bladder and stomach showed numerous purpuric lesions but both organs had been intubated prior to death. The bowel contained tarry material and there were petechiae in the small intestine.

The significant microscopic lesions were confined to the capillaries and small arterioles, many of which were distended and filled with a hyaline material identical in appearance with that in Case 1. There was no surrounding inflammatory reaction. In some areas the plugged vessels were surrounded by recent hemorrhage. Some of the thrombosed vessels were being recanalized. In some vessels the endothelial cells were swollen and projected into the lumen. The vascular lesions were most numerous in the heart. There were areas of necrosis scattered throughout the cardiac muscle but no fibrosis such as was present in Case 1 was observed. The involved vessels in the adrenals were principally near the cortical surface, while in the kidney they were more frequent in the capillaries of the glomerular tufts. The involved vessels and hemorrhages in the pancreas were located in the lobules and interlobular spaces. Scattered vessels were also involved in the liver, spleen, brain, bladder and gastrointestinal tract. The diagnoses were: (1) thrombotic thrombocytopenic purpura; (2) congestion of lungs, liver, spleen, kidneys, adrenals and brain.

COMMENTS

The manifestations in these two cases were different yet the basic histopathologic lesion was identical. Our second patient showed the characteristic clinical picture of thrombotic thrombocytopenic purpura with the diagnostic triad of hemolytic anemia, thrombocytopenic purpura and transient neurologic manifestations. Because of this a correct antemortem diagnosis was made. The diagnosis was more difficult in our first patient who had a very complex and prolonged illness. The clinical course was characterized by recurrent thrombophlebitis, pulmonary infarctions and refractory leg ulcers probably due to stasis. As the condition progressed the picture suggested disseminated lupus erythematosus although attempts to confirm the diagnosis by demonstrating "L.E. cells" were unsuccessful. Even at autopsy the gross finding of a verrucous endocarditis was

thought to support the diagnosis of lupus. However, the microscopic findings did not substantiate this diagnosis and showed the characteristic vascular lesions of thrombotic thrombocytopenic purpura. The failure to find significant thrombocytopenia and the lack of hemorrhagic manifestations are also of interest. Many platelet counts were normal. The last platelet count done two days before death was 289,000, which is only a slight reduction. The patient did have ecchymotic urticarial lesions but this was at a time when the platelet count was normal and he gave a history of a similar eruption several years previously. The absence of hemorrhagic manifestations has been noted in other cases.[5,6]

The cause of this disorder is unknown. Baehr and his co-workers[2] suggested an allergic basis because of the resemblance of the vascular lesions to those occurring in the Shwartzman phenomenon. Fitzgerald and his co-workers[3] commented on the frequency of urticaria in patients with this disease. One of their patients had severe hives intermittently for a year prior to death. Sulfonamide sensitivity was noted in the case reported by Engel[7] and iodine sensitivity was believed responsible for the condition in the case reported by Erich and Seifter.[8] Both of our patients showed penicillin hypersensitivity. The relationship of these hypersensitivity reactions in our patients to the development of the disease is uncertain. In our second case the patient was told that he was anemic before the injection of penicillin and therefore it is possible, although not certain, that the condition may have antedated the reaction. We believe, from the appearance of the lesions in our first case, that they developed as a terminal event and thus followed the penicillin administration. In any case the frequent occurrence of drug hypersensitivity in this disease is probably more than coincidental.

The relationship of thrombotic thrombocytopenic purpura to disseminated lupus erythematosus has been discussed by others. Most authors have denied any relationship[2,6,9,10] although Gitlow and Goldmark[11] and more recently Beigelman[12] have considered the possibility favorably. Beigelman has suggested that differing syndromes would result depending on the part of the vessel which acted as the shock organ. A reaction in the intima would result in platelet thrombosis; a reaction within the vessel wall, in periarteritis nodosa; and a reaction in the perivascular mesenchyme would result in lupus erythematosus. It is of interest in this connection that non-bacterial verrucous endocarditis similar to that seen in disseminated lupus was found in our first patient. This finding has also been noted in previously reported cases.[2,7,13]

The disease is more common in females. A review of the literature reveals that there have been twenty-two females and twelve males reported, including our cases. The ages of the reported cases have varied between nine and a half and sixty-nine years.[2,13] Over half the cases have occurred in the second and third decades of life. The race was stated in twenty-seven of the reported cases and seven cases occurred in negroes.

Histologically, the pathognomonic lesion is the so-called platelet thrombus which is widely disseminated throughout arterioles and capillaries of practically every organ in the body. Most authorities believe that the hyaline material which partially or completely occludes the vessels consists of agglutinated platelets.[2,6] In fact, the name of thrombotic thrombocytopenic purpura was suggested to indicate that the thrombocytopenia was due to loss of platelets from the circulation due to these platelet thrombi.[4] This supposed platelet origin of the hyaline lesions is based on exclusion of other substances such as hemoglobin, erythrocytes, leukocytes, hemosiderin, collagen or fibrin.[3] It has been further supported by the similarity of the staining properties of these lesions with those of platelets. As Meacham and his coworkers[14] point out, final proof that the hyaline masses are really platelets must await further study and they are of the opinion that most if not all of the material "represents an intramural degeneration rather than an intraluminal coagulum." In this connection it is noteworthy that our first patient had large numbers of thrombi despite minimal thrombocytopenia. Proliferation of the endothelium has been noted around the thrombi. Occasionally foci of necrosis or infarction[15] have been present but these have been insignificant when compared to the widespread distribution of the vascular lesions. Originally it was concluded that there was no evidence of a primary vascular disease.[2] Later it was believed that primary vascular damage in the form of endothelial swelling was responsible for the secondary deposition of platelet thrombi.[9,10] More recently Gore[6] has described focal vascular lesions of the capillaries

and arterioles which he considers primary. Orbison[16] noted similar changes. Similar lesions were found in our two cases, particularly in Case II. In focal areas the vessel walls showed degenerative changes similar in appearance to fibrinoid necrosis. When one could trace the vessels to the point of hemorrhage, the wall was found to be fragmented. Dilatation and thinning of the walls of the involved vessels was also noted in both of our cases. Orbison considered these dilatations to be aneurysms. In skip serial sections of the heart in Case II involvement of almost every vessel was noted. Microscopic focal necroses and hemorrhages were plentiful. The lesions seen were frequently of different ages, suggesting showers of thromboses. In Case I there were recent thromboses with adjacent hemorrhages but the most prominent findings were the numerous foci of fine fibrosis, hyaline perivascular fibrosis and degeneration of the cardiac muscle fibers. In Case II there were areas of recent hemorrhage and necrosis. In both cases the heart was the organ most extensively involved.

The clinical course is usually acute with sudden onset of fever, weakness, pallor, jaundice and hemorrhagic manifestations. Although the jaundice is usually mild, it may be severe.[17] The patient may complain of joint pains which may be indefinite or may simulate rheumatoid arthritis. Abdominal pain without significant localization has occurred frequently. These latter two symptoms are not infrequently seen in patients with hemolytic anemias especially in crises. The hemorrhagic manifestations include petechiae, ecchymoses and hematuria. Moderate hepatomegaly and splenomegaly are usually present. The central nervous system manifestations are most important in pointing to the correct clinical diagnosis and are present in practically every case. These may be present at the onset and dominate the clinical picture or they may occur later, usually complicating what appears to be a hemorrhagic disease or anemia. This occurred in Case I in which the patient had neurologic symptoms including transient tremor only in the last days of life. Adams and his co-workers[18] have recently reviewed the various central nervous system manifestations. These may include hemiplegia, facial paralysis, aphasia, convulsive seizures, tremors or reflex changes. These may be permanent or transient, the latter being especially striking and important in establishing the diagnosis. There may be irrationality, restlessness, confusion, delirium, stupor or coma. The clinical picture may be suggestive of encephalitis.[19] In some patients a psychosis may be the presenting or major manifestation.[20,21] An interesting feature in Case I was the development of paroxysmal auricular tachycardia which might have been due to the extensive cardiac involvement. It is of interest that cardiac manifestations have been rarely described despite the severity of cardiac lesions.

The blood picture shows a hemolytic anemia and thrombocytopenia. A leukemoid reaction may be present and manifested by the presence of nucleated erythrocytes and immature leukocytes. Spherocytosis may be present but is variable. Reticulocytosis is frequent. Singer[22] studied the bone marrow in this disease and found that 57 per cent of the megakaryocytes were producing platelets. He concluded that the manufacture of platelets was not inhibited. On the other hand Meacham and his co-workers[14] found platelet formation to be inhibited. Our first patient showed a normal marrow early in his course. Undoubtedly this antedated the development of thrombotic thrombocytopenic purpura which we believe was a terminal event. The marrow in our second patient showed inhibition of platelet formation. A differential count of 100 megakaryocytes in this case showed 3 per cent megakaryoblasts, 14 per cent promegakaryocytes, 75 per cent megakaryocytes without platelet formation and 8 per cent free megakaryocytic nuclei. No megakaryocytes producing platelets were seen. This agrees with the observations of Meacham and supports his opinion, in which we concur, that the decrease in circulating platelets may be due more to inadequate formation than to their disappearance into platelet thrombi.

The differential diagnosis is from other conditions which may produce hemolytic anemia and thrombocytopenia. Hereditary spherocytosis is seldom associated with severe thrombopenia and hemorrhagic manifestations. A positive family history is also helpful in differentiating the two conditions. Acquired hemolytic anemia is occasionally associated with thrombocytopenic purpura but may be ruled out by the positive Coombs test which is found in such cases and by the absence of central nervous system manifestations. Paroxysmal nocturnal hemoglobinuria is characterized by hemoglobin in the morning urine, which disappears from urine passed later

in the day; leukopenia is frequently present and the acid fragility test is positive. Hypersplenic conditions must be differentiated but these may show a leukopenia whereas the leukocyte count in thrombotic thrombocytopenic purpura is usually elevated. In idiopathic thrombocytopenic purpura, central nervous system manifestations if present are due to extensive cerebral hemorrhage resulting in hemiplegia or death; they do not show the bizarre or transient manifestations seen in thrombotic thrombocytopenic purpura. The anemia in idiopathic thrombocytopenic purpura is proportionate to the amount of bleeding and is never as low as it is in thrombotic thrombocytopenic purpura except when extensive blood loss has occurred.

The prognosis is extremely poor. All reported cases have terminated fatally, usually in a few days to several months. In Beigelman's[12] Case I and in our first case the exact time of onset of the disease was uncertain. This raised the question of atypical cases with longer courses. Engel and co-workers[7] noted a transient improvement in their case but relapse occurred a month later and the patient died about three months after the onset of illness. Meacham et al.[14] have recently reported an unusual case in which there is no doubt that the disease lasted for three years. Their patient underwent splenectomy three years before her death. A remission occurred and the patient was asymptomatic although somewhat anemic. Three years later the patient was readmitted to the hospital with neurologic symptoms and died several months later. Review of the sections of spleen showed typical lesions of thrombotic thrombocytopenic purpura. This would indicate the possibility of milder forms of the disease which do not conform to the classical picture.

Treatment has thus far been unsuccessful. Penicillin did not show any beneficial effect in our first case and, in fact, reactions to penicillin may have precipitated the disease in our cases. Aureomycin was unsuccessful in Case II and also in Singer's experience.[22] Splenectomy has been attempted in six cases.[2,7,13,14,23] Of these patients all but one died during or shortly after operation; it is true that most of them were moribund by the time splenectomy was considered. Muirhead[23] believes that splenectomy has not had a fair trial. A remission apparently was induced in the previously mentioned case reported by Meacham et al.[14] Probably splenectomy deserves further consideration in patients in whom the diagnosis can be made early. We used ACTH without benefit in Case II. Meacham et al. thought that ACTH may have induced a transient remission in one of their cases. This experience is insufficient to draw any definite conclusions.

SUMMARY

1. The clinical and pathologic observations of two cases of thrombotic thrombocytopenic purpura are presented.

2. This condition is characterized by the clinical triad of (1) hemolytic anemia; (2) thrombocytopenic purpura and (3) mental and neurologic abnormalities which may be bizarre or transient. It is not as rare as is generally considered.

3. The disease is of unknown etiology although probably related to hypersensitivity and usually runs a rapid, fatal course.

4. The characteristic histopathologic finding is the widespread plugging of capillaries and arterioles by hyaline lesions.

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The Hemostatic Defect in Thrombocytopenia as Studied by the Use of ACTH and Cortisone*

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THE role of the platelet in the coagulation process and in the preservation of vascular resistance to trauma has long been recognized but the mechanisms involved in each of these phenomena and the factors controlling platelet production and function have not yet been completely elucidated. It has been repeatedly observed that improvement in hemostasis and vascular resistance may occur following splenectomy despite persistence of thrombocytopenia in patients with thrombocytopenic purpura.[1] In addition, surgical procedures other than splenectomy have been observed to produce transient hemostatic improvement in patients with purpura while surgery in non-hemorrhagic states frequently is followed by platelet rises.[2] Robson[3] has demonstrated that non-specific, stress-producing agents may induce increased vascular resistance as measured by the negative pressure method in normal individuals. Other reports in the literature[4–6] indicate that patients with thrombocytopenic states respond well to the administration of ACTH and cortisone with resultant increases in platelet production and improvement in vascular resistance. In view of the apparent relationship between adrenocortical function and platelet production and vascular resistance, this investigation was undertaken in an attempt to determine whether or not these two phenomena are causally related or whether humoral factors may separately influence platelet production and vascular integrity. Included in these studies are observations on the effect of splenectomy when superimposed upon adrenocortical stimulation.

METHODS

Eight patients were studied, five with idiopathic thrombocytopenic purpura and three with purpura and thrombocytopenia associated with leukemia. After suitable control periods and observations seven of these patients were studied during and after the administration of adrenocorticotropic hormone or cortisone. Daily blood platelet and eosinophil counts were done by the methods of Pohle and Pilot, respectively.[7,8] Capillary fragility tests were carried out using standard 13 cm. cuff pressures of 100 mm. of mercury for ten minutes or pressures midway between systolic and diastolic pressure if the former was under 100.[9] The petechiae in a circle of 2.5 cm. diameter located 5 cm. below the antecubital fold were counted following tourniquet pressure. In patients on whom tourniquet tests were performed daily and previously induced petechiae were present, the petechiae were counted in the 2.5 cm. circle before the tourniquet was applied and again after the ten-minute application. The difference between the second and the first counts comprised the number of new petechiae. Clot retraction was measured by Aggeler's method[10] by which procedure abnormal retraction is 20 per cent or greater. Prothrombin utilization was determined as described by Quick.[11] To simplify the recording of prothrombin utilization we have used a ratio of plasma prothrombin time in seconds to serum prothrombin time in seconds. The range of this ratio for normal bloods has been found to be between 0.46 and 0.73. Although such a ratio has no bearing on the absolute prothrombin concentration in the

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plasma, it does reflect the fact that the greater the utilization of prothrombin in the original blood coagulation, the greater will be the serum prothrombin time. A fall in the ratio thus indicates improved prothrombin consumption or utilization. Bleeding times were measured by the method of Duke.[12] Urinary 17-ketosteroid determinations by the method of Drekter et al.[13] were carried out in two patients.*

TABLE I

IDIOPATHIC THROMBOCYTOPENIC PURPURA

PLATELET COUNT AND VASCULAR FRAGILITY DATA ON PATIENTS RECEIVING ACTH OR CORTISONE

Patient	Age and Sex	Diagnosis	Therapy Dose/Day	Days of Study When Given ACTH or Cortisone*	Highest Platelet Count before Therapy (Day)*	Highest Platelet Count during or after Therapy (Day)*	Petechiae (Tourniquet Test)		Remarks
							Before Therapy (Day)*	During Therapy (Day)*	
B. H.	13, F	Idiopathic thrombocytopenic purpura	ACTH 100 mgs.	15 (4–18)	52,000 (4)	115,000 (15)	30 (1)	9 1 (8) (14)	Relapse 2 days after ACTH stopped
			150 mg.	12 (24–35)	51,000 (22)	715,000 (35)	43 (24)	0 (26)	Remission until 30 days after ACTH stopped
			150 mg. then cortisone maintenance	5 (74–78) (79)	35,000 (69)	386,000 (81)	55 (69)	7 1 (75) (78)	Begun on cortisone 125 mg. daily then 50–75 mg.
B. H.	13, F	Idiopathic thrombocytopenic purpura (second study)	Cortisone 50–75 mg.	105 (1–15 wk.)	75,000 (1)	No change	11	No change	Cortisone 125 mg. during menses; tourniquet test positive after cessation
			ACTH 150 mg.	8 (1–8)	44,000 (1)	24,000 (4)	65 (1)	31 (3)	ACTH begun after 30 days without hormone, splenectomy with remission of at least 6 months
S. B.	15, F	Idiopathic thrombocytopenic purpura	ACTH 100 mg.	10 (4–13)	49,000 (2)	438,000 (11)	90 (1)	5 0 (7) (10)	Remission maintained 1 year after therapy
J. K.	49, M	Idiopathic thrombocytopenic purpura	ACTH 150–100 mg.	21 (29–49)	40,000 (1)	32,000 (43)	50 (1)	14 1 (34) (44)	Splenectomy on 46th day with sustained remission for at least 6 months
D. K.	65, F	Idiopathic thrombocytopenic purpura; relapse 6 years after splenectomy	Cortisone 200 mg.	10 (7–16)	12,000 (1)	13,000 (13)	65 (6)	20 10 (13) (14)	Relapse 4 days after cortisone stopped
			ACTH 100–120 mg.	32 (21–53)	25,000 (21)	87,000 (36) 81,000 (44)	52 (21)	10 5 (23) (28) 3 (44)	Relapse 2 days after this course; poor response to ACTH retreatment with smaller dosage
			ACTH 40 mg.; cortisone 100 mg.	16 (61–76)	35,000 (60)	46,000 (77)	41 (61)	21 (69)	Moderate relapse when ACTH stopped and cortisone continued, subsequent remission while cortisone continued and thereafter; mental confusion on cortisone

* Parentheses indicate days of study

RESULTS

Idiopathic Thrombocytopenic Purpura. Four of these patients were studied during either ACTH or cortisone administration and it is apparent that improved capillary resistance occurred with hormonal therapy regardless of the occurrence of a corresponding improvement in the platelet count. (Table I.) In only two patients, B. H. and S. B., were platelet rises noted which corresponded with vascular resistance improvement and in these it may be noted that the latter preceded significant rises in the platelets. In these patients clot retraction and prothrombin utilization ratios improved simultaneously with the increases in platelets.

After each of the first two courses of ACTH in patient B. H., relapse occurred although the second course produced a clinical remission of approximately thirty days' duration. (Fig. 1.) The third course of ACTH then produced a

* We are indebted to Dr. Charles W. Lloyd for these assays.

rapid remission and oral cortisone therapy was initiated. Maintenance cortisone was continued in this patient over a period of approximately sixteen weeks in doses of 50 to 150 mg. daily. (Fig. 2.) Platelet counts remained low and poor clot retraction and elevated prothrombin utilization ratio were present throughout this interval although normal vascular resistance was maintained. Excessive flow during menstrual periods seemed to be controlled by increasing the dose of cortisone to approximately 125 mg. daily in this patient. Because of the

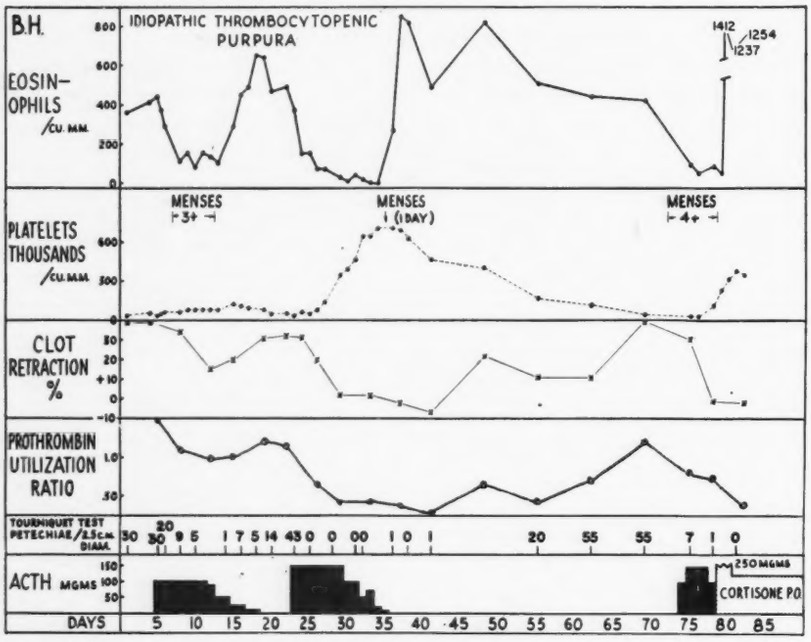

FIG. 1. Patient B. H., idiopathic thrombocytopenic purpura. Temporary remissions during ACTH therapy. Improvement in capillary fragility (decrease in petechiae) precedes significant rise in platelet count.

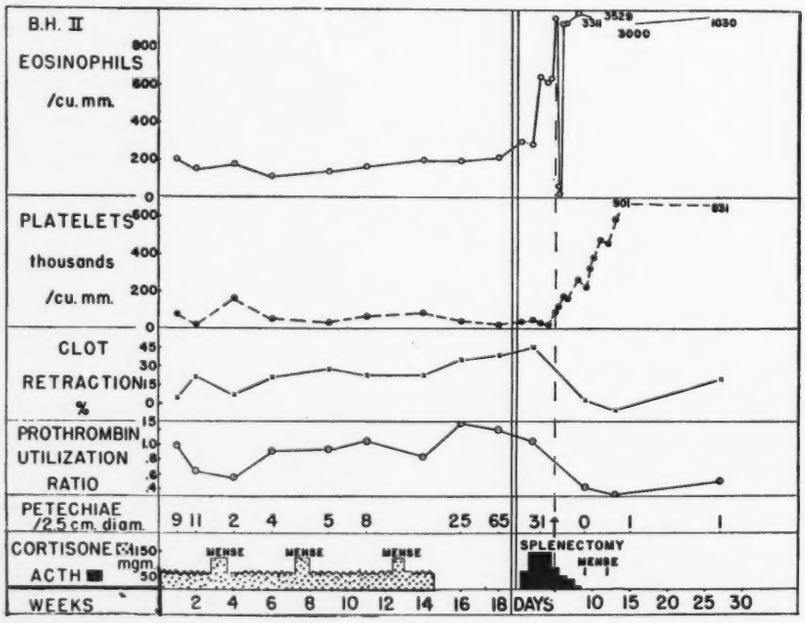

FIG. 2. Same patient, maintenance cortisone therapy with small numbers of petechiae despite low platelet counts. Splenectomy resulted in complete remission which has persisted.

occurrence of hirsutism, skin striae and early rounding of the facies during this interval, splenectomy was elected. After three weeks without hormone, ACTH in doses of 150 mg. daily was given for four days prior to surgery. At this time no platelet response to ACTH was obtained and a rising eosinophil count occurred. No explanation for this resistance to the hormone except for the possible use of an impotent preparation can be offered. On the fifth day splenectomy was carried out without incident. An immediate fall in eosinophils and a rise in platelets with subsequent corresponding improvement in clot retraction and prothrombin utilization took place with concomitant improvement in vascular resistance. A normal menstrual period ensued without excessive bleeding and the patient has remained well for six months after splenectomy.

In patient S. B. the rapid remission occurring during ACTH therapy has apparently been sustained over a one-year follow-up period. (Fig. 3.) The third patient, D. K., a previously splenectomized sixty-eight year old woman, showed marked improvement in the tourniquet test and in spontaneous bruising during the course of cortisone without improvement in platelets, clot retraction or prothrombin utilization. A mild exacerbation occurred as measured by the tourniquet test after cortisone was stopped and ACTH was initiated on the twenty-second hospital day. (Fig. 4.) This brought about a prompt improvement in this patient's tourniquet test, again without change in platelets or other laboratory findings. Cessation of ACTH therapy was also followed by an exacerbation in capillary fragility which was not controlled until after approximately ten days of combined ACTH and cortisone therapy. ACTH was then discontinued with a second

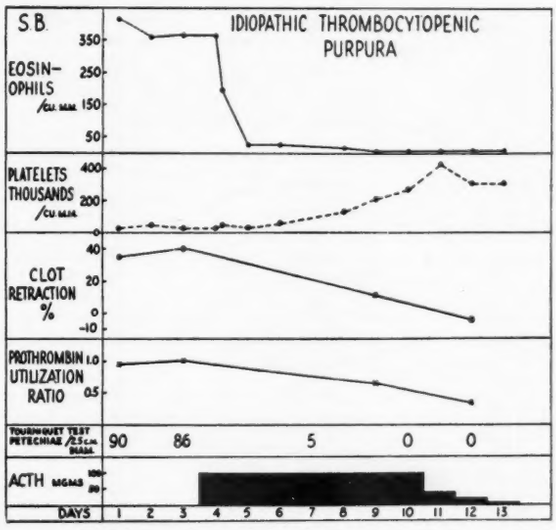

FIG. 3. Patient S. B., idiopathic thrombocytopenic purpura. Tourniquet test returned to normal before marked rise in platelets; remission maintained after ACTH stopped.

relapse despite continued administration of approximately 100 mg. of cortisone daily. Shortly after this the patient underwent a spontaneous remission with a rising platelet

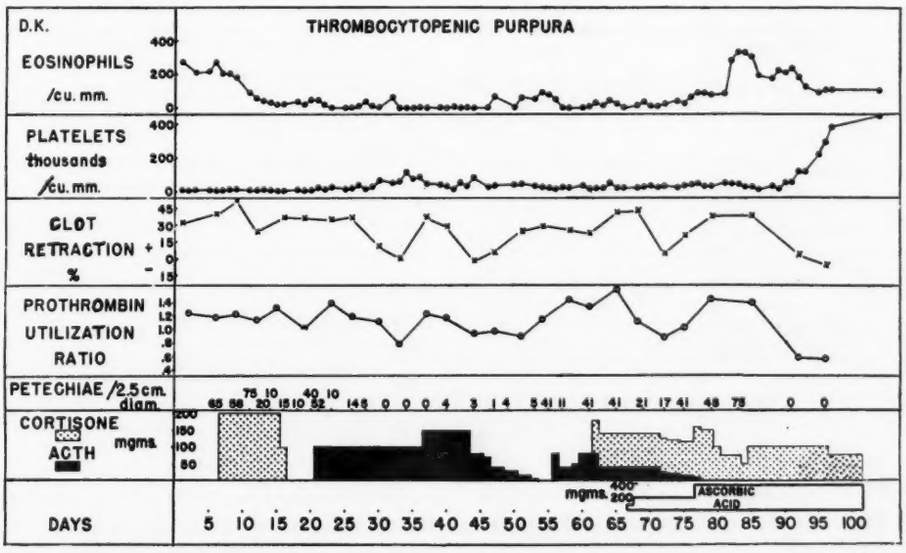

FIG. 4. Patient D. K., idiopathic thrombocytopenic purpura. Control of vascular fragility during ACTH and cortisone despite persistent thrombocytopenia; spontaneous remission occurred during cortisone.

count, improvement in clot retraction and in prothrombin utilization ratio accompanied with return to normal in vascular resistance. This patient's course suggests that the administration of cortisone and ACTH were temporarily useful in tiding her over an acute relapse of therapy. (Fig. 5.) The administration of ACTH for seventeen days before splenectomy in this patient resulted in a prompt fall in tourniquet test without significant change in platelet count or other coagulation functions. Splenectomy produced sustained improvement.

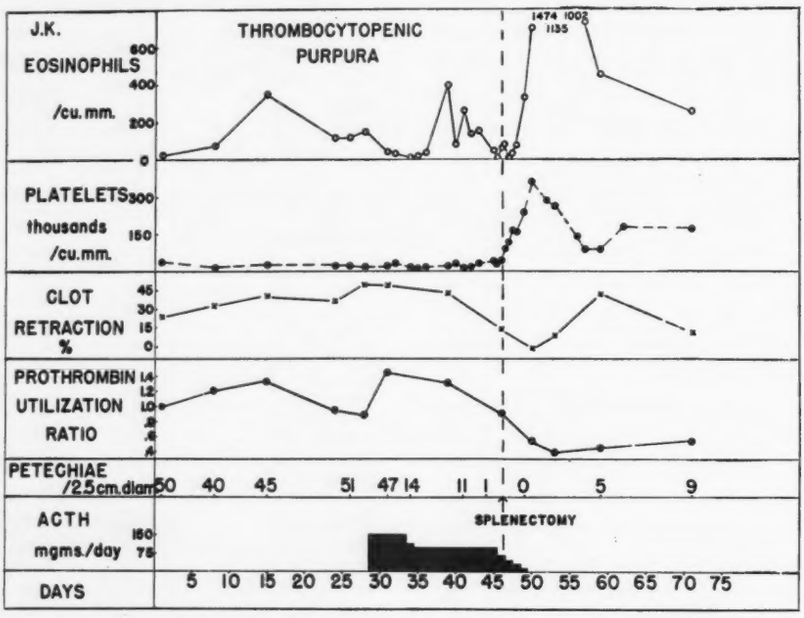

FIG. 5. Patient J. K., idiopathic thrombocytopenic purpura. Improvement in tourniquet test during ACTH without platelet rise; remission followed splenectomy.

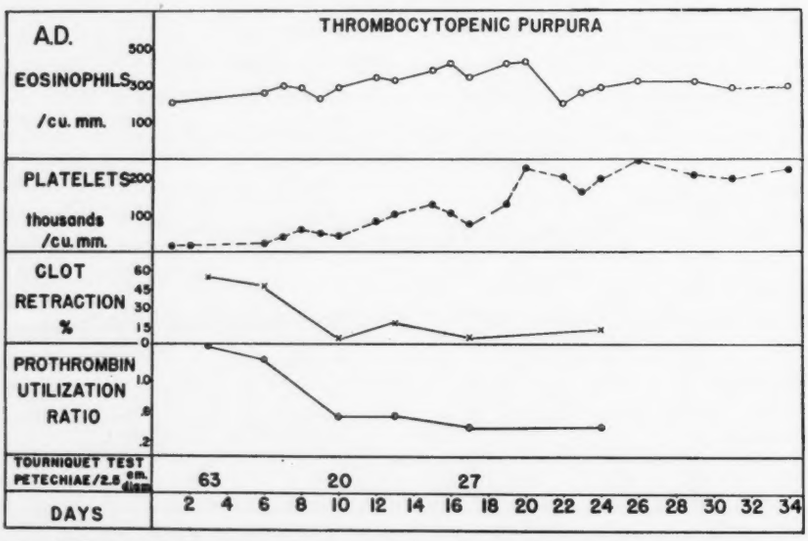

FIG. 6. Patient A. D., spontaneous remission in thrombocytopenic purpura without therapy.

thrombocytopenic purpura. The subsequent remission cannot, however, be attributed to either of these agents.

J. K., a forty-nine year old male, had persistent thrombocytopenia for one month before

Patient A. D., an elderly white woman, was found to have thrombocytopenic purpura which may have been allergic in type, but no specific agent could be definitely incriminated. Over a two-week period of observation the patient

underwent spontaneous improvement in tourniquet test, platelet count, clot retraction and prothrombin utilization. (Fig. 6.) The data on this patient are included to demonstrate the similarity of remission under ACTH therapy to the recovery which may occur spontaneously in this disease.

TABLE II

PLATELET COUNT AND VASCULAR FRAGILITY DATA ON PATIENTS RECEIVING ACTH OR CORTISONE LEUKEMIA WITH THROMBOCYTOPENIA

Patient	Age and Sex	Diagnosis	Therapy Dose/Day	Days of Study When Given ACTH or Cortisone*	Highest Platelet Count before Therapy (Day)*	Highest Platelet Count during or after Therapy (Day)*	Petechiae (Tourniquet Test)		Remarks
							Before Therapy (Day)*	During Therapy (Day)*	
H. H.	58, M	Chronic monocytic leukemia, thrombocytopenia	ACTH 100 mg.	12 (4–15)	52,000 (1)	37,000 (11)	25 (4)	7 (8)	Relapse in tourniquet test after ACTH stopped
M. K.	45, M	Acute myelogenous leukemia, thrombocytopenia	ACTH 40 mg.	3 (3–5)	47,000 (1)	54,000 (5)	50 (3)	12 (5)	Received A-methopterin during study; relapse in tourniquet test after ACTH stopped
G. G.	34, M	Acute aleukemic myelogenous leukemia, thrombocytopenia	ACTH 40 mg., intravenously	4 (1–4)	16,000 (1)	5,000 (3)	65 (1)	34 (3)	Marked relief of gum bleeding; retreatment 30 days after 1st course
			ACTH 40 mg., intravenously	3 (1–3)	11,000 (1)	14,000 (4)	50 (1)	20 (4)	Marked relief again

* Parentheses indicate days of study

Leukemia. To one patient with chronic monocytic leukemia and two with acute myelogenous leukemia ACTH was administered during periods of severe thrombocytopenia and purpura. In all three no change in platelet count occurred although vascular resistance improved markedly. (Table II.) The typical findings of one patient are demonstrated in patient M. K. (Fig. 7.) Withdrawal of ACTH in all patients was followed by a prompt return of the purpuric manifestations. Although relief was but temporary, striking diminution in blood loss from gums and mucous membranes as well as in the purpura occurred in patient G. G. when given ACTH. Drainage of a subphrenic abscess was accomplished without excessive bleeding in the patient with chronic monocytic leukemia and severe thrombocytopenia.

ACTH and Splenectomy. In two patients, B. H. and J. K., splenectomy was carried out during ACTH therapy. As previously mentioned ACTH produced no fall in eosinophils in patient B. H. and only a slight fall in the number of petechiae after a tourniquet test. Patient J. K. also demonstrated an indefinite eosinophil response to ACTH but there was marked improvement in the vascular resistance. (Fig. 5.) Splenectomy* was carried out during ACTH therapy in both subjects and the dosage of the hormone was gradually decreased postoperatively. In both patients no excessive bleeding occurred during the operative procedure and a good response to splenectomy followed. There was no evidence of delayed wound healing in either patient.

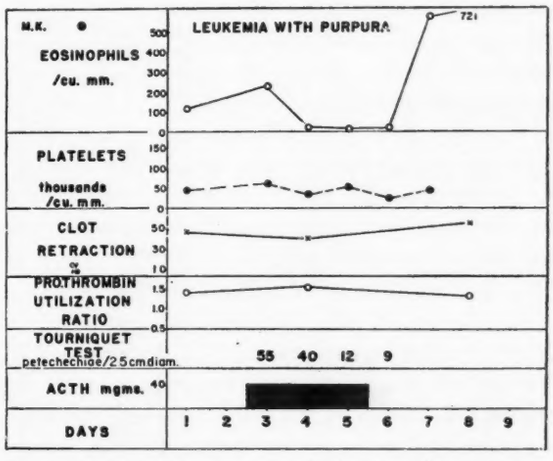

FIG. 7. Patient M. K., acute leukemia with purpura. Improvement in tourniquet test during ACTH without platelet rise.

COMMENTS

Previous work by Robson and Duthie,[3] and Bethell et al.[6] have suggested that capillary

* Surgery was performed by Dr. Leon Berman (B. H.), and Dr. Richard Eberle (J. K.).

resistance improves prior to or in the absence of a rise in platelet counts in patients with thrombocytopenia treated with ACTH. In our series of studies this finding has been a consistent one both in "idiopathic" thrombocytopenic purpura and in patients with thrombocytopenia and leukemia. Although the mechanisms involved in the improvement of vascular resistance without change in platelet counts cannot be clearly defined, it is of note that Menkin[14] and others[15] have found that vascular "permeability" as measured by transudation of fluid in animals is decreased by the administration of cortisone and adrenocortical extract. It has been shown that adrenocortical hormones are able to inhibit the effect of leukotaxin, cell free exudates and hyaluronidase in increasing vascular "permeability." However, there is no clear evidence indicating that vascular fragility represents the same phenomenon as vascular permeability or that either leukotaxin or hyaluronidase are related to petechiae formation.

Another possible mechanism of increased vascular resistance in patients receiving ACTH or cortisone involves the action of ascorbic acid in preserving vascular integrity. Cortisone and ACTH have been found to prolong life and decrease hemorrhagic phenomena in guinea pigs given scorbutogenic diets.[16,17] Plasma and blood cell levels of this vitamin are increased and urinary excretion of ascorbic acid is reduced by cortisone.[18] ACTH, however, has been reported to increase urinary loss in the majority of patients while blood levels of vitamin C are increased or unchanged.[19] The source of the increase in ascorbic acid in the blood is not yet clear but it has been suggested that it is released from certain tissues and deposited in others under the influence of adrenal hormones.[18] It would appear, however, that if this vitamin is involved in the observed improvement in vascular resistance in purpura, on the basis of our studies it must be demonstrated that ascorbic acid metabolism is altered in the same direction by both ACTH and cortisone. In one patient in our series, D. K., who demonstrated suggestive escape of vascular fragility during cortisone therapy, the administration of ascorbic acid in doses of 400 mg. daily resulted in no demonstrable improvement in vascular fragility and a blood ascorbic acid level just prior to this therapy was found to be 0.85 mg. per cent. A spontaneous remission in the patient's disease occurred shortly after the institution of ascorbic acid treatment but no causal relationship could be demonstrated. It is of interest that Stefanini and Rosenthal found hemorrhagic phenomena occurring during the administration of large doses of ACTH which they attributed to ascorbic acid deficiency.[20] No patients in our series have demonstrated this finding.

The studies reported here are of some interest in relation to current theories concerning the etiology of thrombocytopenic purpura. Evans and his co-workers[21] have postulated that there is a relationship of thrombocytopenia to immune mechanisms such as those found in acquired hemolytic anemia. The effect of ACTH and cortisone in altering body reaction in certain hypersensitive states has been demonstrated[22] and it is reasonable to hypothesize that this may be the manner in which remissions are induced by ACTH in thrombocytopenia. The failure of platelet counts to rise consistently during adrenocortical stimulation or substitution therapy, however, casts some doubt upon the theory of hypersensitivity as a cause of thrombocytopenia in at least the idiopathic form of purpura. If the hypersensitivity involves the capillary wall, however, the effect of ACTH and cortisone may be reasonably explained as due to adrenal steroid alteration of an immune mechanism.

It is of some interest in connection with the theory of hypersensitivity in "idiopathic" purpura that both ACTH and cortisone have been found to induce remissions in allergic purpura with or without thrombocytopenia.[23,24]

Harrington and his co-workers[25] have recently demonstrated a thrombocytopenic factor in the blood of eight of ten patients with idiopathic purpura and in one of three subjects with secondary thrombocytopenia. That such a factor might exist had been suggested by the previous studies of Epstein et al.[26] in congenital thrombocytopenic purpura. In two of the patients reported by Harrington the effect of ACTH and cortisone on the thrombocytopenic factor was studied. The thrombocytopenic factor was found to persist in one patient whose platelets failed to change during administration of either hormone. In a second patient cortisone therapy was accompanied with a rising platelet count and disappearance of the thrombocytopenic factor. Interpretation of these results in connection with our studies is difficult but it appears that the platelet reducing factor is only irregularly influenced by these endocrine substances. Our results in regard to thrombocyte response

are consistent with this conclusion. The more consistent occurrence of improved vascular resistance suggests that platelet production or destruction and vascular resistance are controlled at least in part by separate mechanisms. That thrombocyte levels are also of significance in controlling vascular fragility, however, is suggested by the work of Hirsch and Gardner.[27] They have found that infusion of platelet rich blood into thrombocytopenic patients alters vascular fragility toward normal. Unless such infusions contain or stimulate the production of humoral substances capable of improving vascular resistance, their studies and ours indicate that vascular fragility is subject to alteration by either platelet elevation or adrenal steroid mobilization.

One of the theories of thrombocytopenia in patients with idiopathic purpura is that platelet utilization is increased due to the large numbers of bleeding areas and increased demand for platelets.[28] In view of the finding of diminished petechiae formation and the absence of hemorrhagic phenomena with no change in platelet counts during hormone therapy, this theory would appear to be untenable. Failure to find increased platelet counts when petechiae and purpura are controlled would suggest that the thrombocytopenia is due to mechanisms other than increased utilization at bleeding sites.

Emphasis has been placed by some workers upon the fact that idiopathic thrombocytopenic purpura in adults occurs most frequently in females[29] and estrogens have been suggested as a possible causative agent in this phenomenon.[30] In connection with this concept it is of interest that ACTH and cortisone are masculinizing hormones. Whether this characteristic of these agents is responsible for the beneficial effect during their administration, however, cannot yet be answered.

Regardless of the mechanism responsible for the antihemorrhagic effect of the adrenocortical steroids, the therapeutic implications of these studies seem clear-cut. In thrombocytopenic states ACTH or cortisone appear to be beneficial in: (1) tiding patients over an acute episode of thrombocytopenia; (2) preparing patients for splenectomy or other surgery; (3) therapy of persistent or recurrent thrombocytopenia and purpura after splenectomy; and (4) in symptomatic therapy for secondary purpura associated with other blood dyscrasias.

SUMMARY

1. Four patients with idiopathic thrombocytopenic purpura and three with purpura and thrombocytopenia associated with leukemia have been studied during ACTH or cortisone therapy.

2. The results indicate that these agents induce improvement in vascular resistance which is not necessarily accompanied with increased platelet production. Although complete remission with normal platelet counts, prothrombin utilization and clot retraction occurred in two patients, this was preceded by improvement in vascular resistance in both. In all other patients vascular resistance increased without platelet count changes.

3. Administration of adrenocorticotropic hormone or cortisone interferes with neither the occurrence of a spontaneous remission nor remission induced by splenectomy.

4. The hematologic changes occurring during ACTH induced remission do not appear to differ from those found during a spontaneous remission.

5. The use of adrenocorticotropin or cortisone in thrombocytopenic states has been found to control the hemorrhagic phenomena before splenectomy and may be of use in the acute phase until spontaneous remission occurs. Likewise, patients undergoing relapse after splenectomy may undergo improvement during ACTH or cortisone therapy. These agents also appear to be of value in the symptomatic relief of leukemia patients with thrombocytopenia and hemorrhagic diatheses.

CONCLUSION

The hemostatic defect in thrombocytopenia appears on the basis of these results to be twofold: (1) abnormal vascular fragility which has been consistently responsive to adrenocortical steroid mobilization or administration; and (2) reduced production or increased destruction of platelets with concomitant poor clot retraction and prothrombin utilization which are only irregularly corrected by hormone therapy. It is concluded that platelet production and vascular resistance may be separately influenced by humoral factors.

Acknowledgment: The following contributed valuable technical assistance in these studies: Mrs. Jeanne Gilmore, Mrs. Maxine Gabel, Mr. Paul Gabel and Mr. Philip Cholet.

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The Effect of Corticotropin (ACTH) and Cortisone on Idiopathic Thrombocytopenic Purpura*

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A REMISSION has been observed in five of twelve patients with idiopathic thrombocytopenic purpura following the administration of ACTH and cortisone. In three patients the remission has been continuous. In the other two the response was transient. A splenectomy was done in six of the seven patients not responding to the hormones, an excellent result being obtained in five instances.

The effects of ACTH and cortisone on idiopathic thrombocytopenic purpura have not been reported extensively. Bethel et al.[1] observed clinical and hematologic response with ACTH and cortisone in six patients. Rosenberg et al.[2] observed a remission in one of two patients. Wintrobe et al.[3] reported moderate improvement in one case with ACTH, the results being more marked following splenectomy. Harrington et al.[4] and Evans and Liu[5] have each reported an excellent response in a case of postsplenectomy recurrent thrombocytopenic purpura, one patient receiving ACTH and the other cortisone. Hyman[6] reported two subjects responding to these hormones, one to ACTH and the other to cortisone.

Current concepts of the pathogenesis of idiopathic thrombocytopenic purpura postulate that the low platelet levels result from a suppression of megakaryocytic activity,[7] an increase in platelet lysis,[8] or phagocytosis.[9] The recent observations of Evans et al.[10] seem to indicate that platelet agglutinins may be found in the blood of patients with this disease. Harrington et al.[4] have demonstrated the presence of a thrombocytopenic factor in the blood of thrombocytopenic patients. The effects of the pituitary-adrenal systems on the platelets have been observed experimentally. Bilateral adrenalectomy in rats results in a steady rise in the platelets. Platelet levels in hypophysectomized rats are lower than in control animals. A variety of stimuli of stress, such as fever,[13,14] severe exercise,[15] anoxia,[16] hemorrhage,[17] trauma[18] and surgery[19] are reported to alter the platelet level significantly. The beneficial effects of ACTH and cortisone on certain patients with acquired hemolytic anemia in which there is a positive Coombs test are well known. Is it possible that these hormones effect an unknown immunothrombocytopenic mechanism?

METHODS

In each subject the diagnosis of idiopathic thrombocytopenia purpura was made on the basis of the criteria of Wiseman, Doan and Wilson[9] as follows: spontaneous purpura, decrease in blood platelets below 100,000 per cu. mm., the presence of normal clotting time and prothrombin time, anemia and leukocytosis not out of proportion to the amount of bleeding, absence of pathologic cells in the blood or bone marrow, exclusion of history or drugs that are known to cause purpura, and absence of an enlarged spleen or enlarged lymph nodes. Repeated observations were made on the leukocyte, erythrocyte, hemoglobin and blood platelet levels. Platelet determinations were done by a modification of the Rees-Ecker method, normal values in our laboratory ranging from 225,000 to 325,000 per cu. mm. Bone marrow biopsies were done by the aspiration method and studied by the supravital method, Janus green and neutral red dyes, after having been prepared with Wright's stain. Cortisone was given in the following doses: 50 to 100 mg. daily for at least fourteen days. If a

* From the Department of Medicine, University of Kansas School of Medicine, Kansas City, Kan. This study was supported in part by a grant-in-aid from the U. S. Public Health Service.

platelet response was obtained, the dosage was decreased gradually and then discontinued. ACTH was given in doses of 40 mg. per day intramuscularly (or its equivalent in intravenous therapy, 10 mg. per day given in an eight-hour period). A splenectomy was done in those cases not responding to hormone therapy.

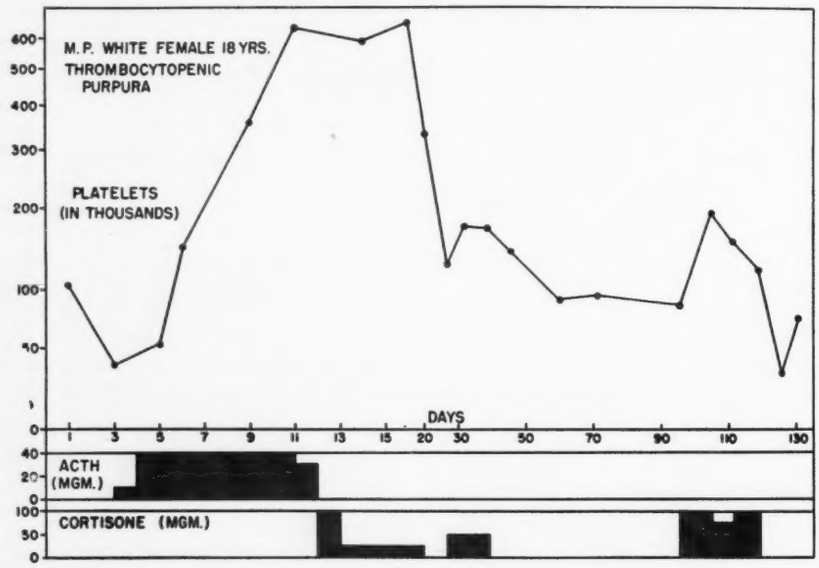

FIG. 1. This patient had a splenectomy four years before with no increase in platelets. Low platelet values had been observed continuously during the four-year period. The patient was admitted with acute pyelonephritis. Response to ACTH was prompt and dramatic; there was little or no response to cortisone.

OBSERVATIONS ON PATIENTS RESPONDING TO ACTH AND CORTISONE

Five patients, four women and one man, had a complete clinical and hematologic remission following the therapeutic administration of ACTH or cortisone. Each patient will be discussed separately because of individual differences in response.

One patient, (Fig. 1) a white woman aged eighteen years, had been observed continuously following unsuccessful splenectomy four years prior to this admission. During this time the platelets had never been above 100,000 per cu. mm. She was admitted to the Medical Center with acute pyelonephritis. The platelets decreased to 36,000 and severe epistaxis and purpura developed. ACTH therapy intramuscularly was started and the platelet response was dramatic and all hemorrhagic manifestations disappeared. The platelets decreased when ACTH was stopped. Subsequently cortisone had little effect.

A white woman, (Fig. 2) aged sixty-two years, was admitted to the Medical Center with acute generalized purpura of three weeks' duration. She had bruised easily for four years. ACTH was given intramuscularly. The platelets became elevated after the fourteenth day of therapy. The hormone was then discontinued and splenectomy was done while the platelets were still elevated. The immediate postoperative response was excellent for a number of days. At a later date all the clinical and hematologic signs of thrombocytopenic purpura recurred.

A white girl (Fig. 3), aged six years, was admitted to the Medical Center with acute thrombocytopenic purpura of three weeks' duration. She had bruised easily since birth. An excellent response to ACTH was obtained. When the hormone was discontinued, the platelets decreased. The patient again responded to ACTH with an increase in platelets and a disappearance of all purpuric signs. The hormone was again stopped. Eighty days later cortisone was given because there was again a moderate decrease in platelets. Since the last administration of cortisone the platelets have remained normal for 430 days of observation and no clinical signs of the disease have occurred.

Two subjects (Fig. 4 and 5), a white boy aged four years with purpura of one week's duration, and a white girl aged four years with purpura of three weeks' duration, were given cortisone

orally and an excellent response obtained in each case. There has been no clinical or hematologic evidence of a recurrence of the disease. The boy has been observed 275 days. The girl has been observed 193 days.

There was a variation in the time interval between initiation of therapy and the platelet response. In three subjects (Fig. 1, 4, 5) the response occurred in less than seven days. In the other two patients (Fig. 2 and 3) the platelets did not increase until the eighth and fourteenth days.

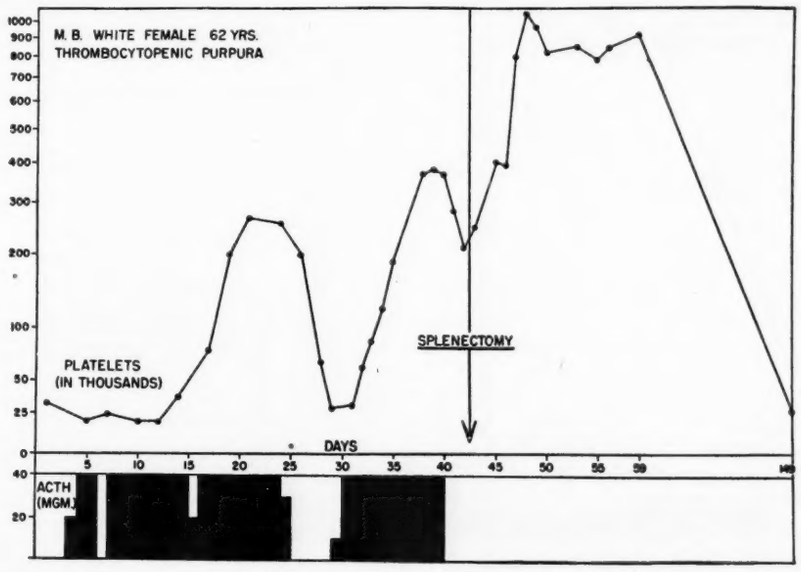

FIG. 2. Patient responded immediately to ACTH. An exacerbation occurred after discontinuing therapy. Again a response to ACTH occurred and splenectomy was done. Immediate postoperative response was excellent but an exacerbation of the disease occurred later.

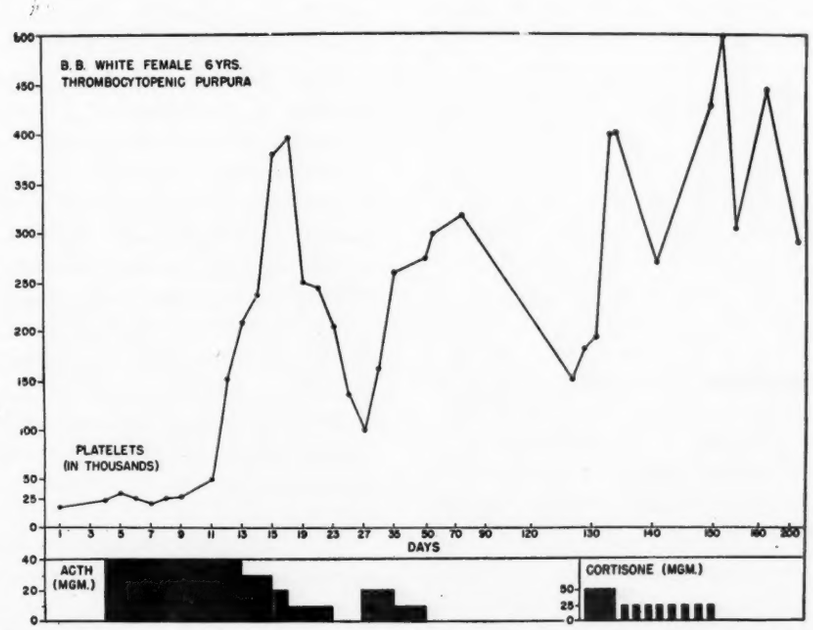

FIG. 3. Patient with immediate response followed by exacerbation after discontinuing therapy. A remission again was produced with ACTH and later with cortisone; remission still persists after 430 days of observation.

OBSERVATIONS ON PATIENTS NOT RESPONDING TO ACTH OR CORTISONE

In seven patients the platelets did not respond to ACTH or cortisone therapy. Four patients were given cortisone and three ACTH. Six were females and one a male. In all but one instance there was a clinical improvement in the purpuric manifestation of the disease, enough so that the patients considered themselves much improved. One subject, a white girl aged nine years, died of cerebral hemorrhage after ACTH had been given for only six days. An adequate evaluation of her case is not possible. Splenectomy was done in the six remaining subjects (Fig. 6) and all but one had an excellent platelet response.

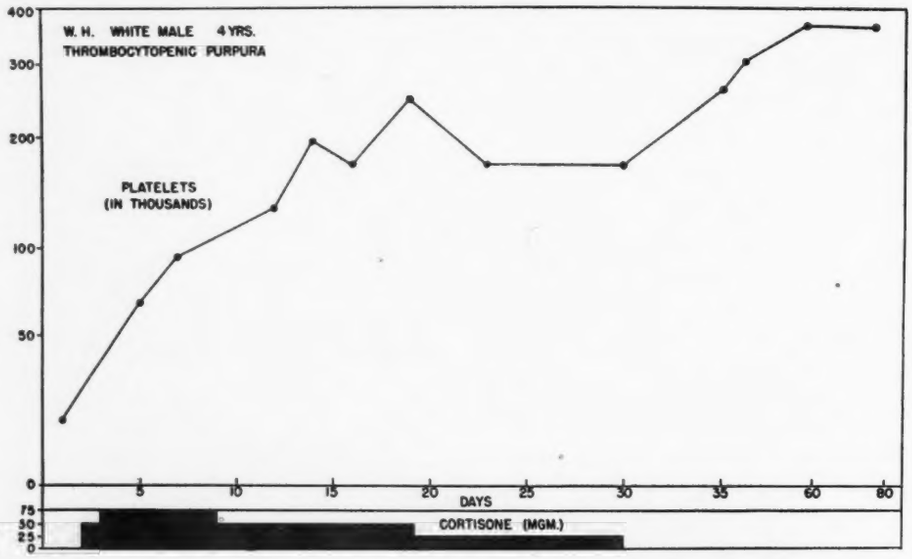

FIG. 4. Response to oral cortisone in a boy with no recurrence following discontinuance of therapy. Thrombocytopenic purpura had been present seven days prior to therapy; no recurrence after 275 days of observation.

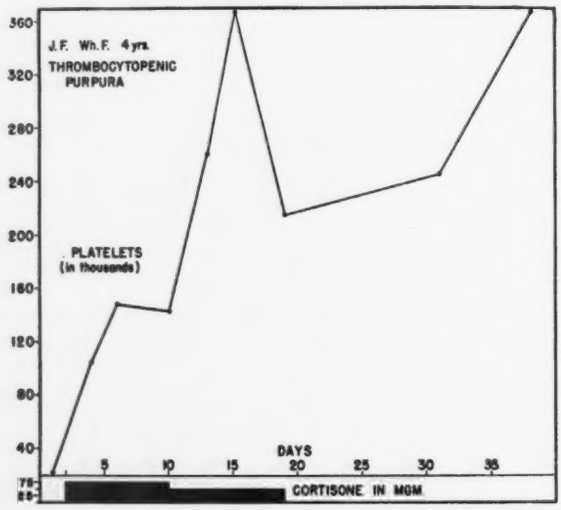

FIG. 5. Prompt response to cortisone in a girl with acute thrombocytopenic purpura; no recurrence has been noted after 193 days of observation.

COMMENTS

It is interesting to speculate on the possible mode of action of the corticoadrenal system on the hematopoietic system. Wintrobe[20] suggests that these hormones act by exerting a regulatory effect on metabolic processes that could proceed even in the absence of these substances. Bethel et al.[1] state that ACTH and cortisone may modify splenic dysfunction in hypersplenism, causing a restoration to normal of platelets in thrombocytopenic purpura.

The current concepts of the pathogenesis of thrombocytopenic purpura have been mentioned previously. Spontaneous remission can occur, which makes evaluation of therapy difficult. The rapid cure of many patients with idiopathic thrombocytopenic purpura following splenectomy cannot be ignored. This would certainly not suggest an immunologic reaction as indicated by Evans et al.[10] Ackroyd[21] concluded that the thrombocytopenia in certain cases of sedormid sensitivity is due to an autoimmune mechanism resulting in platelet destruction. Thus it would seem that there probably is more than one cause for the disease known as idiopathic thrombocytopenic purpura. No discussion would be complete without presenting the recent observations of Wright et al.[22] Direct splenic and venous studies were made in the

hypersplenic syndromes before and after epinephrine. They state that the validity of interpretations relating to selective splenic cellular hypersequestration, as based on epinephrine-induced alterations in the peripheral circulation, has been established by them by carefully controlled splenic artery and vein studies before and after intra-arterial epinephrine injections during the surgical removal of the spleen in selected subjects with either primary or secondary hypersplenic syndrome, including idiopathic thrombocytopenic purpura.

It is difficult to evaluate the actual role of ACTH and cortisone in the control of certain cases of idiopathic thrombocytopenic purpura. It is possible that an "immunothrombocytopenia" is controlled, similar to the excellent effect of these same hormones in certain cases of acquired hemolytic anemia in which the Coombs test is positive. Another interesting hypothesis is that the hormones may directly affect the spleen and the bone marrow. Observations in the next few years will be of interest and importance.

CONCLUSIONS*

Twelve patients with idiopathic thrombocytopenic purpura were administered ACTH and cortisone. Five subjects responded.

One patient who had previously had a splenectomy with recurrence of the disease responded completely to ACTH. Cortisone had little effect on the platelet level. In another subject who responded to ACTH and later had an excellent postsplenectomy response there was subsequent recurrence of thrombocytopenic purpura.

Another patient responded to both ACTH and cortisone. Two others responded to corti-

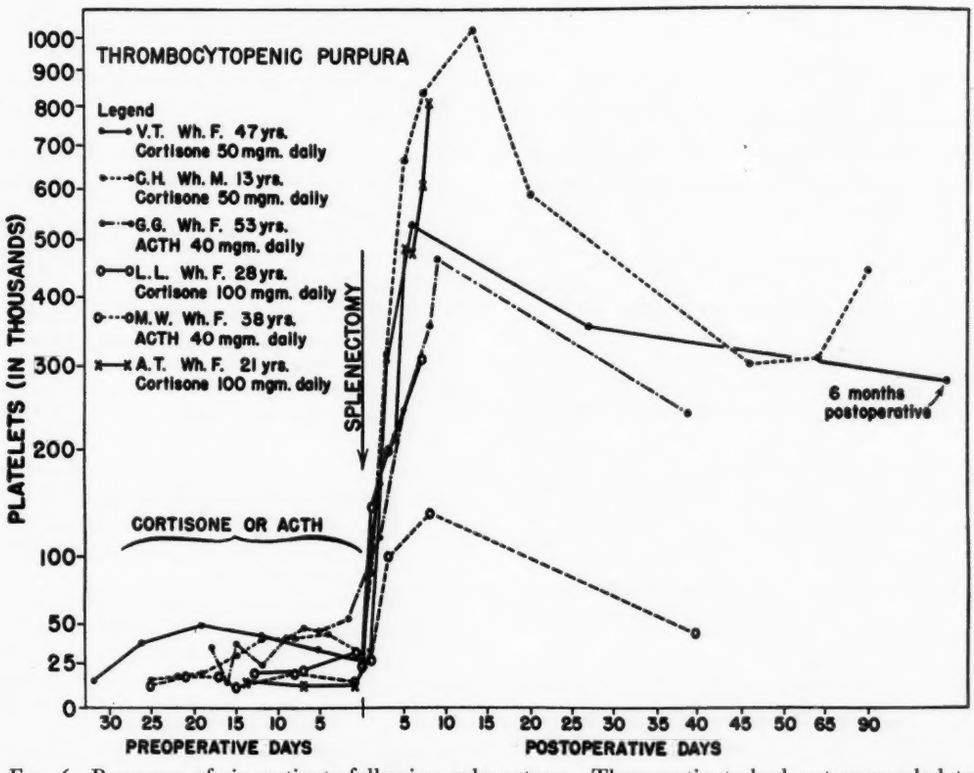

FIG. 6. Response of six patients following splenectomy. These patients had not responded to ACTH or cortisone. One patient had only a slight immediate response with recurrence of the disease shortly thereafter; five subjects responded immediately and dramatically.

* Since submission of this paper for publication, three additional patients have been treated with ACTH and cortisone. Two patients, both four year old white boys, had partial remissions with cortisone and good responses after ACTH. Platelet levels fell to purpuric levels after discontinuation of therapy. In each instance an excellent result was obtained after splenectomy. A nine year old colored girl had a complete remission after the third day of cortisone. M. S. P., the patient in Figure 1, again had a recurrence of purpura which responded to ACTH.

sone. There has been no recurrence of thrombocytopenic purpura in these three patients.

Seven patients did not respond to the hormones. In six instances splenectomy was done, with excellent clinical and hematologic response in five cases.

The mode of action of ACTH and cortisone in certain patients with idiopathic thrombocytopenic purpura is unknown.

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Hypercoagulability of the Blood of Patients with Hepatic Cirrhosis Following Administration of ACTH*

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CONFLICTING reports have appeared concerning the effect of ACTH on blood coagulation. Smith[1] found that ACTH in normal individuals caused a transient increase in coagulation time followed by a slight fall. Cosgriff[2] reported many thromboembolic episodes occurring in patients under treatment with ACTH and cortisone and he found that ACTH frequently caused a decreased coagulation time. Recently, Fahey reported that he found no significant change in whole blood coagulation times in normals and in patients treated with ACTH.[3]

In the course of evaluating the effect of ACTH therapy in cirrhosis certain effects on blood coagulation were observed which have been briefly reported.[4,5] Patients with advanced cirrhosis manifest deficiencies in several of the components involved in blood coagulation, including plasma prothrombin, plasma fibrinogen and blood platelets. In patients with cirrhosis exhibiting these deficiencies thrombotic episodes are a rarity and indeed hemorrhagic manifestations are common. However, while under treatment with ACTH three patients with advanced cirrhosis developed what appeared to be acute portal vein thrombosis. This occurrence suggested that certain of the known deficiencies in the blood clotting mechanism of these patients had perhaps been corrected by ACTH, thus allowing the stagnant portal blood to clot. Accordingly, the effects of ACTH on various phases of blood coagulation were studied in a group of patients with cirrhosis. ACTH caused a decrease in coagulation times even to subnormal levels. No alterations were detected in plasma prothrombin, fibrinogen, antithrombin or blood platelets which could account for the increased coagulability of the blood. The plasma antithrombin levels were found to be subnormal in cirrhosis.

METHODS AND MATERIAL

Fourteen patients with various forms of hepatic cirrhosis were treated with ACTH. Seven of these were given a course of therapy consisting of 60 to 100 mg. a day for at least a week or until complications arose suggesting portal vein thromboses (three patients). The remaining seven patients were given a short course of therapy, usually of two days' duration. The clinical evidence of hypercoagulability of the blood following ACTH therapy is summarized under Case Reports

Plasma prothrombin times were measured by means of a modification of Quick's one-stage method using rabbit lung thromboplastin prepared in this laboratory. Levels of plasma prothrombin were estimated in the conventional way by reference to a control curve of prothrombin times of serially diluted normal plasma. The control was run with each group of determinations and the same subject served as the normal control throughout these experiments. Since most of the patients studied had markedly reduced levels of prothrombin, the 1:8 diluted prothrombin times were too prolonged and variable to be of any value in this study. Fibrinogen was determined from recalcified oxalated plasma by means of acid digestion and nesslerization. Platelets were counted on stained, thin blood smears on cover slips with reference to the erythrocyte count, at least fifty oil immersion fields being examined. Coagulation times were measured by means of the conventional Lee-White three-tube method slightly modified to retard coagulation so that subnormal values could be directly detected.

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The modifications consisted only in using uniform tubes of slightly larger diameter (12 mm. inside diameter) and in tilting the tubes less frequently. Thus the first tube was carefully tilted at five-minute intervals until finally the clot could support the blood in the inverted tube. The second and third tubes then were tested at three- and two-minute intervals, respectively. All of the other usual precautions were observed in drawing and delivering the blood and in having all glassware chemically cleaned. Since the blood coagulation time was being determined in non-coated glass tubes, the syringes and needles likewise were not coated with silicone or oil. By using this method the normal coagulation times determined at 22° to 24°C. ranged from thirty to forty-eight minutes.

Plasma antithrombin activity was determined by a modification of the method of Quick.[6] A standard solution of thrombin* was prepared of such activity that when serially diluted with saline and tested on oxalated normal plasma, the range of coagulation times approximated that suggested by Quick. Thus one lot of powdered thrombin dissolved to contain 100 NIH units per cc. was serially diluted and 0.1 cc. of each dilution was added to 0.2 cc. of oxalated normal plasma and the following coagulation times were found.

Dilution of thrombin solution	Full strength	2×	5×	10×	20×	40×	100×	200×
Coagulation time (sec.)	4	6	10	18	35	62	118	270

These values indicated that this solution of thrombin had the proper activity for use as a standard solution. The same lot of powdered thrombin stored in the refrigerator was used throughout each series of tests, being freshly prepared before each test. The standard solutions prepared and tested in this manner had very similar activity from day to day and thus were satisfactory for detecting any changes in plasma antithrombin activity caused by ACTH. Following the establishment of an appropriate standard solution of thrombin the antithrombin activity of plasma was determined. The oxalated plasma to be tested was defibrinated by adding 0.1 cc. of the standard solution of thrombin to 2.5 cc. of oxalated plasma. The clot was removed and the defibrinated plasma was then tested for its ability to inactivate thrombin. After 0.8 cc. of the standard solution of thrombin was added to 0.4 cc. of defibrinated plasma the solution was incubated at 37°C. At intervals of one, three, five, ten, fifteen, twenty, twenty-five and thirty minutes 0.1 cc. of the thrombin defibrinated plasma solution was removed and added to 0.2 cc. of normal oxalated plasma, and the coagulation time was measured. The coagulation time indicated the relative amount of thrombin remaining in the incubated solution and inversely the antithrombin activity of the defibrinated plasma tested.

* Topical thrombin, commercially available from Parke, Davis and Company, Detroit, Mich.

CASE REPORTS

CASE I. V. V., patient 3, was a sixty-four year old male who had typical advanced Laennec's cirrhosis with ascites. For six days 100 mg. of ACTH was administered daily. On the fifth day the patient had pain, redness and tenderness localized over the left femoral canal. This was considered to be due to a venous thrombosis although the development of thrombosis in such a patient having a prothrombin level of 32 per cent of normal was very unusual. On the next day the signs in the femoral area had subsided but the patient had a fever and a deep diffuse abdominal aching pain and tenderness. The ascitic fluid became bloody and determinations of hemoglobin indicated an intraperitoneal hemorrhage of approximately 300 cc. Administration of ACTH was discontinued. In several days the abdominal signs disappeared. The patient showed no other clinical effects of ACTH therapy. Salt retention, being constantly maximal in this patient, showed no change. Ascites continued to form in direct proportion to the amount of ingested sodium. Ascitic fluid remained free from infection.

Three weeks after this episode the patient had severe esophageal hemorrhages and died. At autopsy the portal vein and some of the mesenteric radicles were found to be completely thrombosed. The thrombosis was of recent origin and seemed to have occurred concurrently with the administration of ACTH.

CASE II. M. H., a woman aged forty-six years, had primary biliary cirrhosis and xanthomatosis for six years. She never had ascites. She received 100 mg. of ACTH daily for three days when suddenly fever and diffuse abdominal pain and tenderness developed. On the following day ascitic fluid, which had never been present

previously, was detected and found to be grossly bloody. The estimated blood loss was replaced by transfusion. In the following week the abdominal pain and tenderness subsided and there was no further evidence of intraperitoneal hemorrhage. However, ascites continued to accumulate and at a maximal rate, exactly proportional to the sodium ingested. This state persisted for two months, the ascites being controlled only by rigid restriction of sodium. Then a spontaneous diuresis occurred and the ascites was absorbed.

TABLE I

LEVELS OF PLASMA PROTHROMBIN AS PER CENT OF NORMAL IN PATIENTS WITH CIRRHOSIS, BEFORE AND DURING ADMINISTRATION OF ACTH

Patient										
1			27	36	37					
2				46	49					
3*			31	36			34		32	
4	48	36	43	42	57	55				
5*				28	23		25			
6				24	35					
7*	30	29	38	35	28		27			33
8*				52		54				
9			40	34	32		47		40	
10				55			60			
11*		37	42	50	37	42		35		
12*		60	60	60	61	60				
	Control values before ACTH				1	2	3	4	5	6
					Days of ACTH therapy completed					

* Patients showed increased coagulability of blood as a result of ACTH therapy.

It is not clear whether ACTH caused a portal thrombosis or an intra-abdominal hemorrhage due to a distended portal bed secondary to retention of salt and water. However, the appearance of ascites for the first time and its persistent accumulation at a maximal rate for over two months after discontinuation of ACTH support the likelihood of a portal thrombosis.

CASE III. D. M., patient 5, was a nineteen year old girl who had an undetermined form of advanced cirrhosis associated with certain manifestations suggesting Cushing's syndrome.[4,5]

The prothrombin was 28 per cent of normal. There was gingival bleeding daily for many months which occurred spontaneously or with slight trauma. Within twelve hours of the first dose of ACTH the gums stopped bleeding. On the fourth day of treatment a diffuse deep abdominal aching and generalized abdominal tenderness suddenly developed, and the blood coagulation time of seventy minutes dropped to eight minutes which is far below the lower level of normal of thirty minutes as determined by the method used. Because of the possibility of portal thrombosis ACTH was discontinued and heparin therapy was begun. The abdominal pain and tenderness subsided and disappeared after several days. No ascites developed. It was of interest that bleeding from the gums did not occur again until six weeks later, despite a return of the coagulation time to former levels immediately after cessation of therapy.

Comments. The aforementioned three cases indicate that ACTH has some effect in enhancing blood coagulation. One of the patients reported on herein gave evidence at autopsy that ACTH caused portal vein thrombosis and the other two patients presented a clinical picture suggesting the same complication. Intermittent gingival bleeding was refractory to the

usual therapy in one of the cases reported (Case III) and in three other patients, and in each of these four cases the bleeding promptly ceased following administration of ACTH.

RESULTS

Plasma Prothrombin. Levels of plasma prothrombin were detected in twelve patients with cirrhosis, both before and during administration of ACTH. (Table I.) In no instance was there evidence of any effect produced by ACTH. Furthermore, evidences of hypercoagulability of the blood attributed to ACTH therapy occurred in the presence of marked deficiencies of plasma prothrombin. (Table I, patients 3, 5, 7, 8, 11 and 12.) This includes patients who as a result of ACTH therapy developed probable portal thromboses (patients 3 and 5), a pronounced decrease in coagulation time (patients 5, 7 and 11) or a prompt cessation of refractory bleeding from the gums (patients 5, 7, 8 and 12).

Plasma Fibrinogen. Plasma fibrinogen was determined in the course of ACTH therapy of six patients with cirrhosis. (Table II.) Four of these six patients showed evidence of increased coagulability of the blood due to ACTH therapy. Changes in plasma fibrinogen were inconstant and did not correlate with the alterations in coagulation time.

TABLE II

PLASMA FIBRINOGEN BEFORE AND DURING ACTH THERAPY

Patient No.	Before Treatment	During Treatment
3*	232 mg. %	248 mg. %
4	343 " " 312 " "	347 " "
7*	218 " " 209 " " "	153 " " 170 " " 160 " "
9	295 " "	280 " "
11*	184 " "	157 " "
12*	583 " "	597 " " 490 " "

* Patients showed increased coagulability of blood.

TABLE III

COAGULATION TIME INDEX

COAGULATION TIME OF PATIENT DIVIDED BY COAGULATION TIME OF CONTROL

Patient					
4		1.3	1.5	1.4	1.3
5			1.8		0.2*
7	2.8	1.9	2.3	1.0*	0.4*
11	1.3	1.1	1.6	1.5	0.25*
12	1.3	1.6	1.3	1.4	1.3
Days before and after onset of ACTH	3	2	1	1	2
	Control values			ACTH	

* Heparin therapy given.

Coagulation Time. The effect of ACTH on the coagulation time was determined in five patients with advanced cirrhosis. (Table III.) The pretreatment values in these patients were generally prolonged but following therapy in

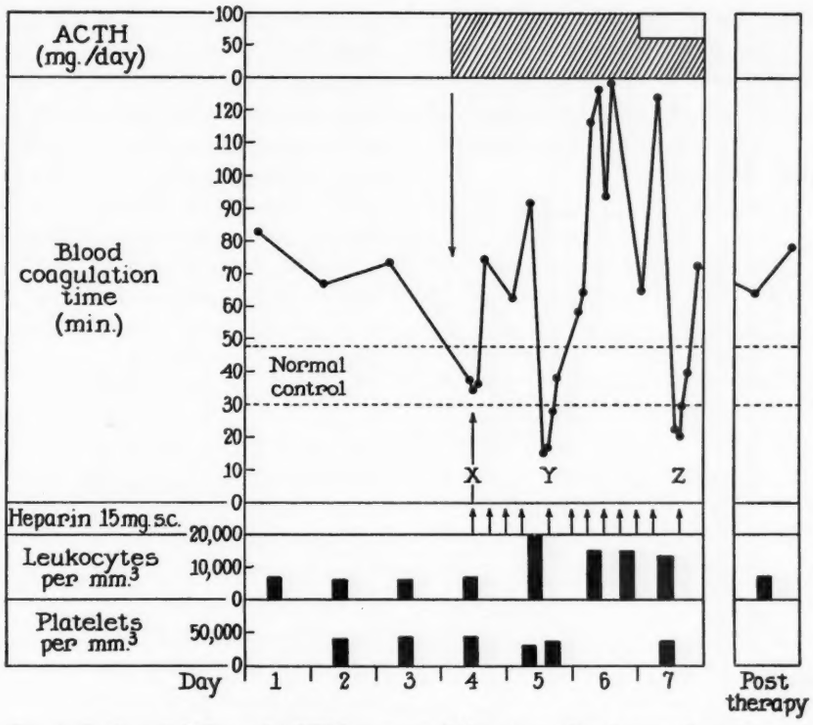

FIG. 1. Patient 7. Effect of ACTH on coagulation time. Ten hours after onset of therapy coagulation time reduced to normal (X). On first and third days thereafter (Y and Z) delay in administration of heparin resulted in subnormal coagulation times; no effect noted on platelets.

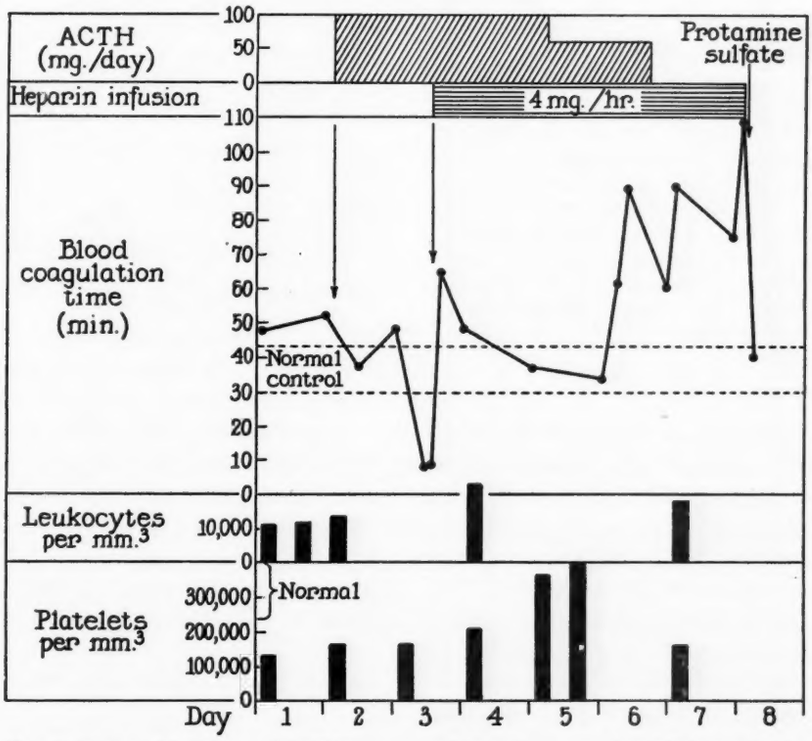

FIG. 2. Patient 11. Effect of ACTH on coagulation time, causing fall in coagulation time to markedly subnormal levels. Rise in platelet count too late to account for accelerated coagulation.

three patients there was a pronounced decrease in coagulation times to markedly subnormal levels (patients 5, 7 and 11). One of the other two patients (patient 12), despite no change in the coagulation time, showed prompt cessation of chronic gingival bleeding.

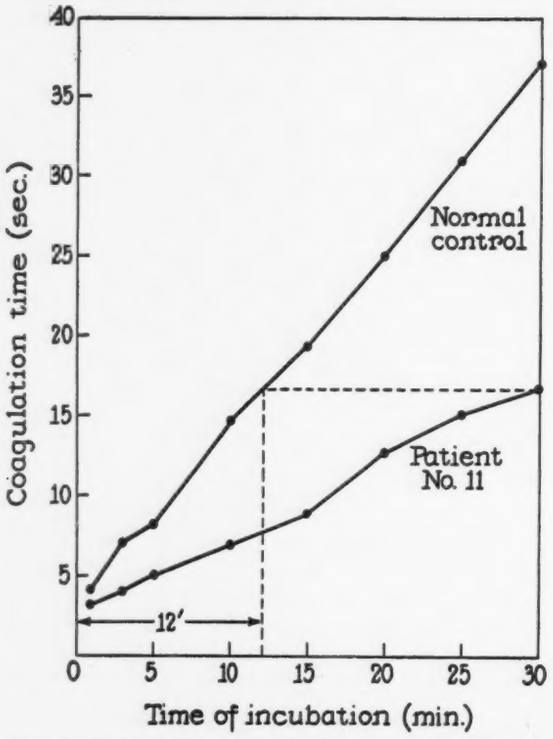

FIG. 3. Patient 11, method of determining plasma antithrombin activity. Ordinate indicates coagulation time of normal oxalated plasma to which is added the thrombin, defibrinated plasma mixture which has been incubated for varying time intervals. Abscissa indicates time of incubation of thrombin, defibrinated plasma mixture. After thirty minutes of incubation the patient's plasma inactivated the same amount of thrombin which was inactivated by the normal control in twelve minutes. The estimate of antithrombin activity is

$$\frac{12 \text{ minutes}}{30 \text{ minutes}} \times 100 = 40\%.$$

The effects of ACTH on blood coagulation time in patients 7 and 11 are illustrated in Figures 1 and 2, respectively. Patient 7 (Fig. 1) had a prolonged coagulation time until ten hours after the onset of ACTH therapy when the coagulation time was found to be normal. Because of this sudden fall in coagulation time heparin was administered intermittently in doses of fifteen mg. subcutaneously every six hours, relatively small doses of heparin having been found to be effective in the presence of cirrhosis. One day later a dose of heparin was postponed and at a period nine hours after the previous injection of heparin the coagulation time was found to have fallen far below the normal range. (Fig. 1.) Two days later a similar delay in administration of heparin had the same effect. A similar effect on coagulation time was noted in patient 11. (Fig. 2.) One day after the onset of ACTH therapy the coagulation time fell to markedly subnormal levels. This patient was then treated with constant intravenous infusion of heparin at the rate of approximately 4 mg. per hour and satisfactory coagulation times were maintained.

Platelets. The relationship of platelet and leukocyte counts to ACTH therapy and blood coagulability is shown in Figures 1 and 2. Both patients had splenomegaly and normal bleeding times. Patient 7 (Fig. 1) had a low platelet count initially and it remained unaltered by treatment with ACTH during periods of large fluctuations in the coagulation time. Patient 11 (Fig. 2), on the other hand, showed a rise in the platelet count from moderately low levels to normal values. However, the fall in the coagulation time occurred before any significant increase was noted in the platelet count. The leukocyte count rose in both cases.

Plasma Antithrombin Activity. The antithrombin activity of plasma of a typical patient with advanced cirrhosis is illustrated in Figure 3. There it is seen that after thirty minutes of incubation of the patient's defibrinated plasma with a standard amount of thrombin the thrombin that was inactivated was equivalent to that inactivated by normal defibrinated plasma in twelve minutes. Hence the patient's antithrombin activity of the plasma is arbitrarily estimated at $\frac{12 \text{ minutes}}{30 \text{ minutes}} \times 100 = 40$ per cent of normal. Plasma antithrombin activity was found to be considerably reduced in most cases of advanced cirrhosis of various types. (Table IV.)

The possibility that the hypercoagulability of the blood noted after ACTH therapy could be associated with altered antithrombin activity was tested and the results are indicated in Figure 4. No change in antithrombin activity was noted following ACTH therapy in four patients with cirrhosis, in two of whom (patients 7 and 11) marked changes in coagulation time had occurred during this test period.

OBSERVATIONS

The complexity of the blood clotting mechanism is emphasized by the results reported,

which showed that blood of cirrhotic patients can become hypercoagulable as a result of therapy with ACTH without any detectable change in the major components of coagulation. Blood hypercoagulability occurred despite persistent deficiencies in certain of the blood clotting factors which are characteristic of patients with advanced cirrhosis and which are often associated with the hemorrhagic tendency of these patients.

The factors concerned in causing blood hypercoagulability remain obscure. Plasma levels of prothrombin and fibrinogen were not increased by therapy with ACTH. Hypersplenism, often present in association with cirrhosis, could account for the reduced platelets frequently found in such patients. ACTH has been effective in the therapy of hypersplenism and its hemorrhagic manifestations.[7] If the platelet count can be used as an index of splenic activity it would appear that in the reported cases the effect of ACTH therapy on blood

TABLE IV

ANTITHROMBIN ACTIVITY OF PLASMA OF PATIENTS WITH VARIOUS FORMS OF LIVER DISEASE

Patient	Diagnosis	Plasma antithrombin % of normal
A. S.	Metastatic Cancer of liver	100
R. P.	Primary Biliary Cirrhosis	100, 100, 100
C. G.	Coarse nodular cirrhosis of undetermined etiology	40, 33, 33
D. M.	"	33, 30, 33
J. G.	"	17, 17, 20, 16, 17, 17
R. P.	Laennecs Cirrhosis	43, 59, 50, 48
A. T.	" "	23
J. A.	Post hepatitis cirrhosis	40

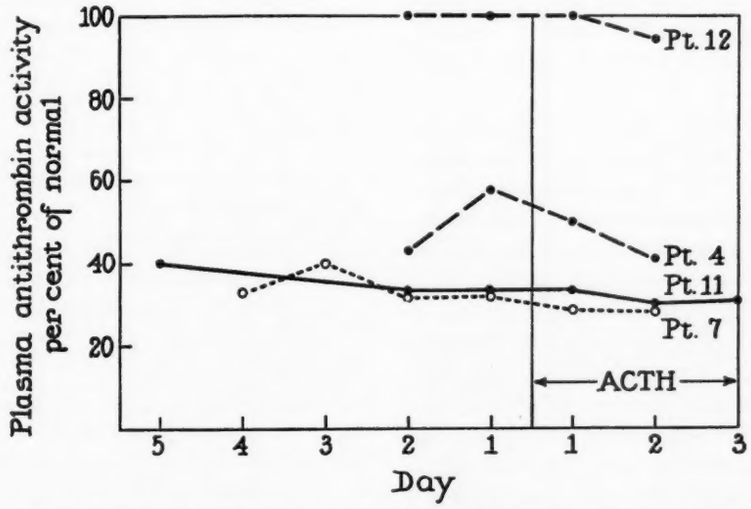

FIG. 4. Effect of ACTH on plasma antithrombin activity in four patients with cirrhosis. Patients 7 and 11 had marked changes in coagulation time. (Figs. 1 and 2.)

clotting was not mediated through a reduction in the degree of hypersplenism. It has been suggested that alterations in plasma antithrombin activity may account for some hypercoagulable states.[8] ACTH therapy caused no change in plasma antithrombin activity indicating that the rate of inactivation of preformed thrombin was not affected. The subnormal rate of inactivation of thrombin which was found in most of our patients with cirrhosis might result in hypercoagulability of the blood following ACTH therapy beyond that found in patients with normal plasma antithrombin, provided that such therapy could cause an increased production of thrombin by increased thromboplastic activity. Cosgriff, however, by determinations of prothrombin consumption found no evidence of increased thromboplastic activity following ACTH therapy in one case.[2] Thus these results in addition to those reported previously[1,2,3] leave unexplained the mechanism of blood hypercoagulability found in patients with cirrhosis treated with ACTH.

Due to the production of accelerated blood clotting precautions might well be taken in the course of therapy with ACTH. Cosgriff recommends the use of anticoagulant therapy. The present results showed that *in vivo* and *in vitro* blood hypercoagulability occurred despite levels of plasma prothrombin approximating 30 per cent of normal. This degree of prothrombin deficiency is considered to be in the therapeutic range in patients receiving anticoagulant therapy with dicumarol. From these results the effectiveness of dicumarol as an anticoagulant to be used prophylactically in the course of ACTH therapy might be questioned. In the patients studied, heparin therapy promptly controlled the hypercoagulable state.

There have been some favorable reports on the therapeutic effectiveness of ACTH in acute and chronic hepatitis.[9,10] In cirrhosis, however, no significant beneficial effects have been reported. The present results suggest that ACTH may represent a distinct hazard to patients with cirrhosis probably because of the association of the relatively stagnant portal blood in cirrhosis and the blood hypercoagulability following ACTH therapy. Administration of ACTH in the presence of cirrhosis may, however, be indicated to help control serious gingival bleeding, provided that careful anticoagulant therapy with heparin is readily available.

SUMMARY

ACTH therapy caused probable portal thromboses in three patients with cirrhosis of the liver. ACTH also caused cessation of gingival bleeding in four patients with cirrhosis and a reduction of coagulation times to subnormal levels in three patients.

Following ACTH therapy, blood hypercoagulability developed in certain patients despite deficiencies in plasma prothrombin, fibrinogen and platelets. ACTH therapy caused no effect on these clotting components which could account for the increased clotting tendency.

Plasma antithrombin activity was found to be subnormal in six of seven patients with advanced hepatic cirrhosis and showed no change during ACTH therapy.

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Chronic Hypoplastic Neutropenia*

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THE normal leukocyte count varies between 5,000 and 10,000 cells per cubic millimeter of blood, and the normal neutrophil level is between 3,000 and 7,000. Values of neutrophils below these figures may be said to represent the neutropenic state. This may be either acute or chronic; one form of the latter condition which appears to be based upon selective hypoplasia of bone marrow granulocytes is the subject of the present report.

The various factors clearly related etiologically to chronic neutropenia have been well described and classified.[1–3] Thus neutropenia may result from a diminished production of granulocytes in the bone marrow, as seen in certain nutritional deficiencies, aplastic anemia and in conditions in which the bone marrow is replaced by abnormal tissue. Reduction in blood granulocytes may also result from a failure of these cells to cross the barrier between the marrow sinuses and the peripheral blood despite normal or even increased production *in situ*. Such a phenomenon of "blocked delivery" is evident in the aleukemic or subleukemic forms of granulocytic leukemia and probably represents the process operative in splenic neutropenia. Increased peripheral destruction or sequestration of granulocytes represents a third possible means by which chronic neutropenia may arise, and it has been postulated by some authors that the splenic form of the disease falls into this category. In certain other conditions with chronic neutropenia the mechanism is at the moment quite obscure. Under this heading may be noted such diverse disorders as disseminated lupus erythematosus, thyrotoxicosis and brucellosis. A special type of neutropenia is the cyclic form characterized by periodic episodes of neutropenia at more or less fixed intervals. Another rare form is that described in the present report which deals with chronic neutropenia, non-splenic, non-cyclic, completely obscure as to etiology and apparently due to specific hypoplasia of the marrow granulocytes.

This condition, which we call chronic hypoplastic neutropenia, has evidently received little attention in the literature. Hattersly[4] described a case of chronic neutropenia without primary disease of the marrow and in which the neutropenia was unaffected by splenectomy. Adams and Witts[5] reported five similar cases, one of which was splenectomized without benefit; the remaining four cases showed none of the stigmas of hypersplenism or of other known etiologic factors responsible for neutropenia. It is the purpose of the present report to add four more cases of chronic neutropenia which were apparently primary disorders of granulocyte production.

CASE REPORTS

CASE 1. (New England Center Hospital No. 51–424.) S. P., a seventeen year old white girl, was admitted to the hospital on July 5, 1950, complaining of a non-healing sore of the left leg.‡

She had been well until the age of seven, at which time she began to have recurrent furuncles which tended to heal extremely slowly. These lesions persisted until two years prior to her admission. In 1943 osteomyelitis of the maxilla developed, and in 1944 an abscess of the mouth. Both these lesions continued to flare up periodically since then and did not heal completely despite extraction of all teeth in 1947 and the extensive use of antibiotics. Episodes of these and other infections were always accompanied with high fever, often over 105°F. In April,

‡ The patient was referred through the suggestion of Dr. John Suess of Pittsburgh by the Social Service Department of the Montefiore Hospital in Pittsburgh. We are indebted to the authorities of that hospital for providing us with their voluminous records of this patient.

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1947, the patient was admitted to the Montefiore Hospital of Pittsburgh with an episode of right upper lobe pneumonia. This improved gradually by lysis over a two-week period with the use of penicillin; no tubercle bacilli were found in the sputum.

Slight splenomegaly and neutropenia were first noted in 1945. By 1947 the spleen had become distinctly palpable and the diagnosis of splenic neutropenia was made. At the suggestion of one of us (W. D.) splenectomy was performed on May 10, 1947. The spleen weighed 850 gm. and was described as having a tense capsule and being firm on section. Grossly it was purplish red in color, with prominent trabeculae and ill defined malpighian bodies. Microscopically the malpighian bodies were completely disrupted. The pulp was replaced by reticulum cells and large histiocytes, and some of the cells contained blood pigment. Most of the sinusoids were empty, the trabeculae were increased in size and the capsule was thickened. It was believed that the findings were those of reticulum cell hyperplasia.

Following splenectomy there was no significant alteration of the white blood cells. In November, 1947, a "granulomatous" lesion of the tongue developed which on biopsy proved to be composed of non-specific granulation tissue. In the latter part of 1948 a mosquito bite of the left shin became secondarily infected and progressed into a large ulcerative lesion which resisted all therapeutic efforts. The patient's growth and development had ceased in 1945 when she was twelve years of age. In December, 1948, it was noted that there was cyanosis and clubbing of the fingers; two weeks later the patient had an attack of pneumonitis of the right lung bases which responded readily to penicillin. In the next year and a half the patient was given repeated blood transfusions as supportive therapy and in an attempt to raise her persistently low granulocyte count. In the year prior to her current admission painless contraction deformities of both knees had developed "incident to inactivity." The patient was admitted to the New England Center Hospital in 1950 for further evaluation.

The past history was non-contributory. Prior to the age of seven the patient had been a "normal, healthy child" having had only chicken pox, measles and mumps. Eight months prior to her present admission there was a single episode of vaginal bleeding but otherwise no evident development of secondary sexual characteristics had been observed.

Physical examination revealed an emaciated, chronically ill and deeply cyanotic young woman who had the general appearance of a twelve year old child. The skin showed numerous scars over the arms, legs and trunk, evidently representing healed furuncles. On the left shin there was an ovoid, superficial ulceration measuring 10 cm. in its greatest diameter and draining purulent material. There were contraction deformities in both knees without evidence of active joint inflammation. The head showed a swelling of the right maxillary region. There was marked congestion of the conjunctival vessels with cyanosis which was seen to involve the retinal vessels as well, and was accompanied by moderate papilledema. The gums were edentulous. Generalized lymphadenopathy involved the cervical, axillary and inguinal nodes. The peripheral lymph nodes were firm, non-tender, freely movable and measured up to ½ cm. in diameter. The heart and lungs were within normal limits. All evidence of sexual development was lacking, including absence of mammary glandular tissue, and axillary and pubic hair. The genitalia were prepubertal in type. The abdomen showed a left upper quadrant scar from the previous splenectomy. The liver was palpated at the level of the umbilicus. Marked clubbing of the fingers and toes was present.

Hematologic data are summarized in Table 1. The outstanding feature was the presence of an extreme degree of neutropenia although the total leukocyte count was itself normal. The bone marrow showed erythroid hyperplasia and a striking paucity of granulocytic elements. The urine contained a faint trace of albumin and a few finely and coarsely granular casts; the specific gravity on casual specimen was 1.021. Stools were negative for occult blood. Blood non-protein nitrogen was 38 mg. per cent and fasting blood sugar 99 mg. per cent. Serum cholesterol was 110 mg. per cent, thymol turbidity 4.6 units, cephalin flocculation test 3 plus, prothrombin time was 12 seconds (100 per cent) and 20 per cent of bromsulfalein was retained in the blood after forty-five minutes. Electrocardiogram revealed no abnormality and the blood hemodynamics were within normal limits. Vital capacity was 2.2 L. (75 per cent of calculated anticipated normal). The blood was negative for methemoglobin and

sulfhemoglobin. Culture of the leg lesion showed a proteus, bacillus, not further identified. The arterial oxygen capacity was 22.8 volumes per cent, with an arterial oxygen of 12.2 volumes per cent or 58 per cent saturation. When pure oxygen was administered by closed system, the arterial oxygen content rose rapidly to normal levels. This was consistent with a diagnosis of pulmonary insufficiency. X-ray examination of the chest showed slight hilar congestion but the heart was normal on films and fluoroscopy. X-ray examination of the hands showed no bony lesions but revealed soft tissue swelling at the terminal phalanges.

The patient's course in the hospital was characterized by the onset of spiking fever eight days after admission, associated with pain in the right ear. Physical examination revealed the presence of acute right otitis media which was brought under control by penicillin therapy. Local application of antibiotics to the leg ulcer appeared to cause some regression of this lesion; at the time of discharge, eleven days after admission, the cyanosis appeared to be somewhat diminished.

Five months following discharge the patient died at the Montefiore Hospital in Pittsburgh. The following autopsy findings are abstracted from the record kindly supplied by the Pathology Department of that hospital. The lungs were grossly congested and the left base was the site of recent infarction. Additional findings microscopically were the presence of alveolar thickening, arteriolar sclerosis and numerous heart failure cells. The heart was dilated but was free from any congenital abnormality or valvular lesion. The liver weighed 1,560 gm. and appeared to be grossly congested; microscopically, congestive changes were seen; in addition there were areas of focal necrosis and lymphocytic infiltration between the portal triads and lobules. A small accessory spleen was found which measured 3 cm. in diameter and microscopically showed proliferation of the reticulum cells, engorged sinusoids but well preserved follicles. The internal genitalia were infantile in type. The bone marrow was markedly hyperplastic but this hyperplasia was confined to the erythroid precursors, granulocytic elements being present in greatly reduced numbers.

Comment. This patient was known to have had neutropenia for at least five years but her symptoms indicated that this abnormality had

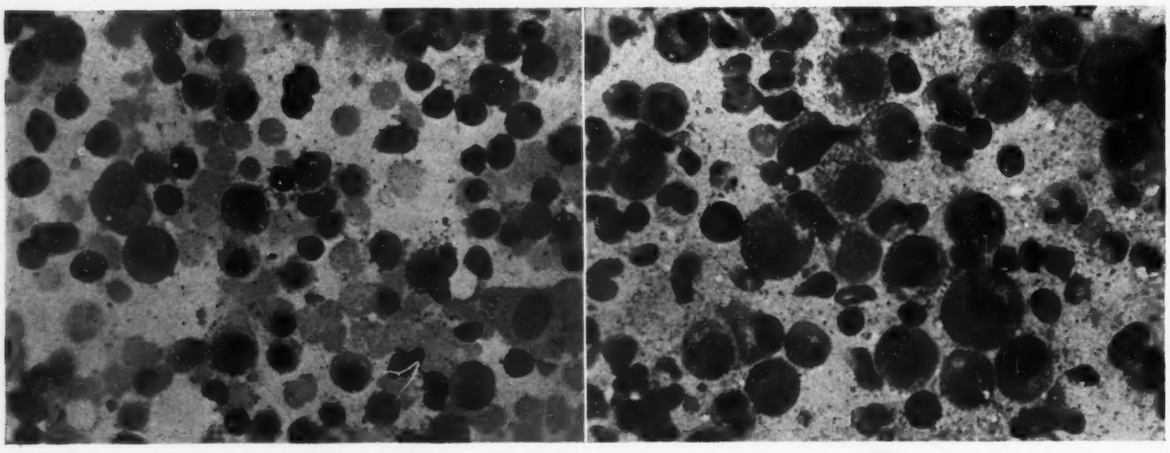
TABLE I

HEMATOLOGIC DATA OF CASE I

Year	Hemoglobin	Platelets	White Blood Cells	Granulocytes		Lymphocytes (Per cent)	Monocytes (Per cent)
				(Absolute Count)	(Per cent)		
1945	54–68%	102,000	4,800–5,750	0–315	0–7	79–95	0–10
1947 (Splenectomy)	9–15 gm.	80,000–186,000	2,500–21,450	0–2,700	0–50	69,100	0–8
1948	11.5–14 gm.	400,000	11,400–17,800	130–2,100	1–12	70–92	0–16
1949	12–17 gm.		9,200–18,440	0–1,360	0–10	87–100	0–3
1950	14–18.3 gm.	142,000–394,000	5,200–16,900	0–1,880	0–22	70–100	0–20

Bone marrow aspiration July 6, 1950. The cellularity was increased but there was a marked paucity of granulocytic elements with erythroid and lymphocytic cells predominating. The megakaryocytes were normal. The following differential count (percentage) was obtained:

Myeloblasts	0.5	Lymphocytes	10.7
Promeylocytes	0.8	Reticulum cells	0.5
Myelocytes	4.0	Plasma cells	6.0
Metamyelocytes	2.0	Pronormoblasts	2.0
Segmented forms	2.8	Normoblasts A	15.5
Eosinophilic myelocytes	0.7	Normoblasts B	41.5
Eosinophils (segmented)	1.2	Normoblasts C	8.7



1A 1B

FIG. 1. The bone marrow pattern of chronic hypoplastic neutropenia compared with that of hypersplenism. A, preparation from Case I (S. P.) showing the almost complete absence of granulocyte precursors and the presence of normal numbers of normoblasts together with increased lymphocytes. B, specimen obtained from a case of splenic neutropenia showing granulocytic hyperplasia and possible maturation arrest at the myelocyte level. The normal myeloid-erythroid ratio is 2:1 to 4:1 by our methods. The range in the present series was 1:1 to 1:4; the ratio in splenic neutropenia is usually greater than 5:1.

probably been present for at least ten years. She had been subject to numerous infections involving the skin, the mouth and throat, the ears, paranasal sinuses and lungs. These had been repeated, severe and prolonged. Her sexual infantilism and lack of growth may have resulted from the chronic state of malnutrition secondary to the numerous infectious processes and perhaps mediated through the pituitary gland. The cyanosis, clubbing of the fingers and erythrocytosis evidently were due to an interstitial and arterial disturbance of the pulmonary tree secondary to the repeated pulmonary infections (Ayerza syndrome). Because of splenomegaly associated with chronic neutropenia, mild anemia and occasional thrombocytopenia, the diagnosis of splenic neutropenia was originally made but splenectomy failed to alter the granulocyte level.

Despite the finding of a small accessory spleen at autopsy this case evidently was not hypersplenic in origin. The lack of any leukocytic response following splenectomy and the specific granulocytic *hypoplasia* of the marrow were strongly against such a diagnosis. (Fig. 1.)

CASE II. (New England Center Hospital No. 44-205.) T. L. D., a sixty-seven year old white man, was first admitted to the hospital on September 28, 1949, complaining of rectal pain. Thirteen months prior to admission he had noted ulcerations of the gums and buccal mucosa. These responded slowly to penicillin but then recurred and persisted intermittently up to the time of admission. In February, 1949, the patient had chills and a fever of 104°F. A course of penicillin therapy was again administered, with temporary remission of symptoms. On August 19th left otitis media occurred, responding to irrigation and drainage; a few days later rectal pain and tenderness recurred, followed later with the development of some difficulty in sphincteric control. Past history and family history were not contributory except that the father was said to have died from "chemical poisoning" after working in a match factory where he had been exposed to sulfur.

Physical examination revealed a well developed, well nourished, elderly white man who showed some evidence of recent weight loss. The right pupil was somewhat irregular but reacted well to light and accommodation; arcus senilis was present. The fundi showed mild arteriosclerotic changes. The mouth was edentulous but no ulcerations were visible. There was a grade I apical systolic cardiac murmur but the heart was otherwise normal on examination. The liver was palpable 2 fingerbreadths below the costal margin and the tip of the spleen was just felt with deep inspiration. Rectal examination revealed a large, purulent fistula and a somewhat enlarged prostate gland. The joints of the knees and fingers showed atrophic changes.

Hematologic findings revealed an extreme degree of neutropenia and bone marrow deficient in granulocytic elements (Table II details

the pertinent data). Other laboratory results included a fasting blood sugar of 95 mg. per cent, negative urines, negative blood cultures and serologic tests for syphilis, and an erythrocyte sedimentation rate of 17 mm. in one hour (Westergren). X-ray of the chest and a flat film of the abdomen revealed no abnormalities.

TABLE II
HEMATOLOGIC DATA OF CASE II

Period	Hemoglobin (gm.)	Platelets	White Blood Cells	Granulocytes		Lymphocytes (Per cent)	Monocytes (Per cent)
				(Absolute Count)	(Per cent)		
Presplenectomy..... (9/28/49–11/11/49)	9.8–14.1	330,000–674,000	800–4,500	0–2,700	0–70	19–80	7–32
Postsplenectomy..... (11/12/49–11/18/49)	12.5–16.3	617,000–837,000	1,100–2,000	0–700	0–64	22–72	0–54

Bone marrow aspiration September 28, 1949. There were areas of increased cellularity as well as other areas of decreased cellularity. The megakaryocytes were increased and 80% of the cells consisted of unidentified nuclei. The following differential count (percentage) was obtained:

Myeloblasts	1.0	Lymphocytes	20.0
Promyelocytes	0.4	Reticulum cells	1.8
Myelocytes	7.0	Plasma cells	1.8
Metamyelocytes	2.0	Pronormoblasts	0.6
Band forms	21.8	Normoblasts A	4.4
Segmented forms	1.2	Normoblasts B	18.4
Eosinophilic myelocytes	1.4	Normoblasts C	17.0
Eosinophils (segmented)	1.0		

Penicillin therapy was administered and on October 1st the rectal fistula was removed; the postoperative course was uneventful. The patient was readmitted October 21, 1949, for further study. Laboratory studies at that time showed a blood non-protein nitrogen of 25 mg. per cent, total plasma proteins 6.5 gm. per cent with 4 gm. of albumin and 2.5 gm. of globulin, cephalin flocculation test 1+, thymol turbidity test 3.4 units and a bromsulfalein excretion test showing a retention of 6 per cent after thirty minutes but no retention after an hour.

The patient was readmitted November 7th. Because of persistent leukopenia and a just palpable spleen the diagnosis of splenic neutropenia was considered; and although this seemed unlikely in view of the marrow findings, splenectomy was performed November 11th. The postoperative course was uneventful despite the persistently low white and neutrophil count.

The splenic pathology was reported as follows: The gross weight was 202 gm. On the surface were several small, shaggy, greyish red adhesions, and a mottled orange trabecular pattern discolored all surfaces. The spleen was firm to section, showing a thickened capsule, but there was no gross evidence of hyperplasia. Microscopically the capsule was the site of healed perisplenitis, the lymphoid follicles showed a complete lack of germinal centers despite their normal size, the vessels were somewhat sclerotic and there was an excessive amount of hemosiderin within the capsule. There was no evidence of increased phagocytosis.

The patient was still alive and fairly well July 1, 1951, although the white cell count remained unaltered.

Comment. This patient had symptoms attributable to neutropenia for over a year, including repeated infections at different sites and recurrent ulcerations of the mouth. A palpable spleen suggested the diagnosis of splenic neutropenia despite the lack of granulocytic hyperplasia in the bone marrow. Splenectomy was performed but failed to cause any change in the neutropenia and the blood picture remained at preoperative levels during the subsequent two years.

CASE III. (New England Center Hospital No. 390-904.) I. T., a sixty-three year old white woman, was admitted April 27, 1949, com-

plaining of intermittent fever of one year's duration. She first became ill in 1913 when she had generalized psoriasis which responded to treatment over a period of several months. In 1923 she had had a severe illness, said to be influenza, which was followed with frequent colds, sinus infections and recurrent furunculosis. with urination occurred. Shortly thereafter furunculosis reappeared, continuing until the time of admission. Urine examination at that time was negative; however, when streptomycin was given, symptoms gradually regressed. Early in April hemorrhoids became evident and about the same time the patient began to have painful

TABLE III
HEMATOLOGIC DATA OF CASE III

Year	Hemoglobin	Platelets	White Blood Cells	Granulocytes		Lymphocytes (Per cent)	Monocytes (Per cent)
				(Absolute Count)	(Per cent)		
1923	65–81%		1,400–4,500	0–740	0.24	75–99	0.10
1948	86–88%		2,100–3,900	203–770	7–24	57–70	0–35
1949	9.0–13.3 gm.	185,000–558,000	700–3,200	0–104	0–8	64–91	4–29

Bone marrow aspiration May 11, 1949. The specimen was hypocellular and showed an almost complete absence of granulopoiesis. Plasma cells and reticulum cells were increased in number but the normoblasts and megakaryocytes were normal.

At that time she was admitted to another hospital in Boston* where she was noted to have marked leukopenia and neutropenia. The presence in the blood of lymphocytosis and atypical lymphocytes occasioned the presumptive diagnosis of lymphocytic leukemia. Several blood transfusions were administered at that time. For the past fifteen years she had noted pain and swelling in the ankle, hip and knee ioints; motion in the right knee had been limited for the past several years. There had been occasional "canker sores" in the mouth.

In October, 1948, she had an upper respiratory infection followed shortly with cough and excessive fatigue. Early in November of the same year she had an episode of severe pain in the right flank radiating to the shoulder and neck, and accompanied by vomiting and fever. At that time she was found to have pyuria. Because of intolerance to sulfonamides, penicillin was administered and she slowly improved. In December, 1948, acute pharyngitis, cervical adenopathy and fever developed; the white blood cell count was again noted to be low. Penicillin was administered, with gradual relief of the symptoms. In March, 1949, a shaking chill, fever, pain in the right flank and burning swelling of the inguinal lymph nodes. On the tenth day prior to admission fever of about 100°F. developed. During the patient's illness she stated that she had lost 50 pounds.

Physical examination revealed a well developed, slightly obese white female not acutely ill. Temperature was 100°F., pulse rate 88 and respirations 20. The skin showed eczematoid dermatitis behind the right ear and a few small furuncles on the face and trunk. Healed scars of the previously noted furuncles were seen over various parts of the body. Arcus senilis was noted in both eyes. The mouth was edentulous. A grade II systolic murmur was heard in the aortic region but the heart was otherwise negative. The abdomen revealed some diffuse tenderness throughout on deep palpation but there was no rigidity or palpable masses. The liver and spleen were not enlarged. Rectal examination showed external hemorrhoids. Pelvic examination was negative. Examination of the fingers revealed Heberden's nodes and there was crepitus in both knees. A slight flexion deformity of the right knee was present but there was no definite evidence of rheumatoid arthritis.

Hematologic data are summarized in Table III. They showed extreme neutropenia with relative lymphocytosis and no alteration of erythrocyte or platelet counts. Other laboratory

* We are indebted to the authorities of the Peter Bent Brigham Hospital for permission to examine the records of this patient.

studies revealed a normal urine, fasting blood sugar of 101 mg. per cent, stools negative for occult blood, serum cholesterol 146 mg. per cent and negative blood cultures. Agglutination tests were negative for brucella, typhoid and proteus but positive for paratyphoid B in a dilution of 1:40. The serology was negative for syphilis. An abscess of the finger was cultured and showed Staphylococcus aureus. Chest films and intravenous pyelography were negative. An incidental finding in the x-ray studies was the presence of coarse trabeculation symmetrically distributed in the pelvic bones, interpreted as Paget's disease. A calcific density was noted in the region of the gallbladder.

During the course of the patient's hospital stay she showed intermittent temperature elevations ranging up to 101.6°F. The fever and furunculosis did not respond to penicillin or to combined streptomycin and aureomycin therapy. The patient was discharged after one month's observation with essentially the same findings as on admission.

She was admitted to another hospital* July 20, 1949, having had a continuation of the previously noted symptoms including anorexia, weight loss, fatigue and night sweats. There a flat film of the abdomen revealed a solitary gallstone and slight splenomegaly. Bone marrow biopsy was reported to show aplasia. During her hospital stay the patient ran spiking temperatures to 105°F., and on blood culture pyocyaneus was recovered. Ulcers noted under the right arm and left groin, and tender right axillary lymph nodes failed to respond to penicillin therapy. Ten days after admission rales developed in the lung bases and the patient became cyanotic and expired.

Postmortem examination revealed the following findings of interest: The liver was moderately enlarged and on microscopic examination showed distention of the sinusoids with blood and periportal infiltration with lymphocytes. Three ulcers, circular, indurated and with a yellow base, were present in the distal ileum. There were basal and lateral adhesions in the right pleura and several black bronchial lymph nodes 1 to 5 cm. in diameter. The lungs were grossly edematous, showing vascular congestion with patchy emphysema and atelectasis on microscopic examination. The heart weighed 440 gm., was dilated and showed fibrous thickening of the endocardium and coronary sclerosis. The aorta was moderately atheromatous. The spleen weighed 390 gm. Its capsule was smooth, bluish and tense. The cut surface was pale and soft, showing diminished pulp but prominent trabeculae and follicles. Microscopically the changes were merely those of congestion; there was no evidence of excessive phagocytosis or myeloid metaplasia. The urinary bladder was the site of a mucosal plaque which was brown centrally, had yellow edges, measured 1.5 cm. across and cut with a "fibrous" consistency. Microscopically this proved to be a granulomatous lesion infiltrated with plasma cells, lymphocytes and giant cells, and contained areas of focal necrosis. The gallbladder contained a large stone but there was no evidence of obstruction. The kidneys showed congestion of the vessels and interstitial infiltration with lymphocytes. The adrenals showed lipid depletion and lymphocytic infiltration around the central vein. Culture of the heart's blood grew out pyocyaneus.

Comment. This patient had an unusually long history of severe neutropenia dating back for at least twenty-five years. It was remarkable in that so few stigmas of the disease had developed during so long a period. Although not disproved, splenic origin of the neutropenia was unlikely because of the striking degree of marrow granulocytic hypoplasia, the absence of splenic disorder and the normal platelet counts.

Case IV. (New England Center Hospital No. 12-031.) M. F., a fifty year old white woman, was admitted to the hospital January 3, 1944, complaining of weakness and dizziness. In the year prior to admission she had noted the gradual onset of vague complaints consisting of "feeling below par," easy fatigability and a weight loss of about 16 pounds. Two months before admission exertional dyspnea developed and a month later weakness became so severe that the patient was confined to bed. At that time x-rays of the teeth revealed apical abscesses, and several dental extractions were performed which were followed by moderately severe bleeding and painful swelling of the gums. Objective vertigo appeared shortly thereafter; this was precipitated by motion of the head and followed by vomiting.

The past history included a prolonged story of repeated psychiatric disturbances including three "nervous breakdowns" the last of which

* We are indebted to the authorities of the Massachusetts General Hospital for permission to publish these data.

had occurred ten years prior to admission, and a menopause characterized by attacks of melancholia. The family and occupational history were non-contributory, nor was any history of exposure to noxious agents elicited.

Physical examination showed the patient to be moderately obese. She did not appear to be either acutely or chronically ill. Pulse, temperature, respirations and blood pressure were within normal limits. The significant findings included carious teeth and gums which were hypertrophied and bled easily. The heart and lungs appeared to be normal. There was no enlargement of the lymph nodes. The spleen was palpated 2 cm. below the costal margin but there was no other abdominal organ enlargement.

The hematologic data are summarized in Table IV. The striking finding was marked neutropenia associated with a normal total white blood cell count and absolute lymphocytosis. The red cells and platelets were within normal limits. The bone marrow was normocellular and was characterized by normal numbers of erythroid elements and megakaryocytes, moderate lymphocytic infiltration and by a marked paucity of granulocytic elements. Other laboratory findings showed a negative serologic test for syphilis, 2+ albuminuria with increased white blood cells in the urine, an erythrocyte sedimentation rate of 78 mm. in one hour (Westergren) and a basal metabolic rate of minus 16 per cent. The total serum proteins were 8.4 gm. per 100 cc., with 3.3 gm. of albumin and 5.1 gm. of globulin.

At the suggestion of Drs. A. White and T. Dougherty* the patient was given intramuscular injections of whole adrenal cortical extract in doses of 20 cc. daily for one week in the attempt to reduce possible lymphocytic hyperplasia and thus increase the granulocytic level. There was no hematologic response and the patient was discharged with essentially the same complaints as on admission. Three weeks later she was again admitted because of persistent symptoms, having had several additional teeth extracted in the interim. Physical findings at that time were similar to those of the previous admission save for increasing enlargement of the spleen which was now felt 5 cm. below the costal margin. X-rays of the abdomen confirmed the splenomegaly. Films of the skull were normal. No specific therapy was instituted and the patient was discharged with unchanged symptoms after a two-week stay. She was admitted for the third time May 9, 1944, at which time no change was noted symptomatically or in the physical or laboratory findings. She was discharged after twelve days with a tentative diagnosis of either chronic lymphocytic leukemia or splenic neutropenia.

TABLE IV

HEMATOLOGIC DATA OF CASE IV (PRE-SPLENECTOMY)

Year	Hemoglobin (Per cent)	Platelets	White Blood Cells	Granulocytes		Lymphocytes (Per cent)	Monocytes (Per cent)
				(Absolute Count)	(Per cent)		
1944	75–90	379,000–718,000	4,400–11,600	0–1,044	0–9	70–91	6–25
1945	80–86		7,250–11,250	79–430	1–5	84–92	5–14
1946			9,900	1,188	12		

Bone marrow aspiration January 4, 1944. The cellularity was normal but the granulocytic precursors were markedly decreased. There was a moderate degree of lymphocytosis but the normoblasts and megakaryocytes were normal. The following differential count (percentage) was obtained:

Myeloblasts	0.4	Lymphocytes	45.6
Promyelocytes	0.4	Plasma cells	1.2
Myelocytes	5.6	Monocytes	1.2
Band Forms	2.0	Normoblasts A	1.2
Eosinophilic myelocytes	7.2	Normoblasts B	9.2
Eosinophils (segmented)	0.8	Normoblasts C	20.4

* Then at Yale University Medical School.

From then on the patient was seen intermittently. Her symptoms of fatigue, dyspnea and vertigo continued in varying intensity but there was little change in the physical findings or in the blood picture. In January, 1945, headaches and "canker sores" of the mouth developed. In March of that year an insect bite of the finger led to a severe local infection, regional lymphangitis and fever. These symptoms responded to penicillin and sulfonamides after a week of therapy but left the patient even more debilitated. The course thereafter was characterized by repeated infections of the skin and urinary tract associated with fever and constitutional signs. In March, 1946, splenectomy was performed at another hospital.* The spleen was found to be enlarged but showed no changes other than those due to congestion. There was no hematologic response following the operation. The postoperative course was characterized by thrombophlebitis of the legs which responded to vein ligation, and by a urinary infection which tended to persist despite antibiotics. The patient was last seen in the spring of 1950, at which time she was in clinical remission although the blood contained virtually no granulocytes. Her course had been continuously punctuated by recurrent infections.

Comment. For eight years this patient was incapacitated by marked weakness and fatigue, and subsequently had the stigmas of chronic neutropenia including recurrent infections and oral lesions. The presence of absolute lymphocytosis, splenomegaly and apparent infiltration of the bone marrow with lymphocytes suggested the diagnosis of chronic lymphocytic leukemia. However, the absence of lymphadenopathy, the presence in the bone marrow of normal erythropoiesis and normal numbers of megakaryocytes with a specific depletion of granulocytic elements, and the failure of any progression of a lymphocytic process were against such a diagnosis. The bone marrow picture and the failure to respond to splenectomy precluded a diagnosis of splenic neutropenia. A striking feature of this case is the specific depletion of granulocytes in the blood with completely normal red cell and platelet levels.

REMARKS

The clinical picture presented by the four cases described seems to fit into a more or less clearly defined syndrome centering about the characteristic feature of the disease, namely, prolonged and severe neutropenia. All the patients showed an extremely chronic course characterized by repeated infections which were relatively resistant to therapy, delayed wound healing and a paucity of symptoms in the intervals between infections. Although the sites of infection varied greatly, the skin and oral cavity appeared to be involved with the greatest frequency. This is similar to the findings in acute agranulocytosis. Physical findings were not characteristic save for the scars of previous inflammatory lesions of the skin and frequent ulcerative lesions of the mouth. Splenomegaly of slight to moderate degree was present in all the cases, and with the presence of an extreme degree of neutropenia, the possibility of splenic neutropenia was usually considered strongly. The neutropenia showed little variability and great chronicity. Absolute lymphocytosis and monocytosis were also noted rather consistently and at times there was slight anemia and thrombocytopenia. Other than the neutropenia, the outstanding feature in every case was the finding in marrow aspirations of marked hypoplasia of the granulocytic precursors, in the presence of an otherwise normal cellularity, relatively undisturbed erythropoiesis, and quantitatively and qualitatively normal megakaryocytes. Other laboratory studies were nonspecific or were related to the effects of supervening infections. Splenectomy when performed did not alter the course of the disease, but specific antibiotic therapy appropriate to the infection appeared to be an indispensable part of management.

The present syndrome seems to bear only superficial relationship to chronic neutropenic states previously characterized. In none of the cases was there any evidence of primary infection or other inflammatory or degenerative disorder known to produce neutropenia. There was furthermore no evidence of a proliferative disease of the marrow such as leukemia or lymphosarcoma, a nutritional deficiency or exposure to noxious agents. Evidence was similarly lacking for excessive destruction or sequestration of granulocytes and for the presence of an arrested development or delivery of these cells.

Clinically the patients closely resembled examples of splenic neutropenia. The presence of chronic neutropenia and an enlarged spleen

*We are indebted to Dr. Melvin Tribeman of Haverhill, Mass., for these data.

as well as the occasional anemia and thrombocytopenia are all features which would fit the picture of that disease reasonably well.[6,7] Such similarity prompted the performance of splenectomy in three of the patients. However, the striking granulocytic *hypoplasia* of the marrow and the failure to respond to splenectomy are important differentiating characteristics. Although the appearance of a hypoplastic marrow has been occasionally reported in splenic neutropenia,[8,9] it should be regarded as exceptional.[10–15] One of the essential features of splenic neutropenia is granulocytic *hyperplasia* of the marrow with or without maturation arrest.

It is possible that cyclic neutropenia may be related to the present condition since it has many findings in common. Patients suffering from that curious periodic syndrome may have persistent neutropenia between attacks[16,17] and their course is unaltered by splenectomy.[17–19] The marrow may likewise be hypoplastic with respect to granulocytic elements.[19] Our patients differed from the reported cases of cyclic neutropenia in that there was no evidence of periodicity.[16–22]

There are several reports in the literature describing cases essentially similar to those presented here. Roberts and Kracke[3] reported a group of patients showing chronic debility and mild, chronic neutropenia with episodes of more severe granulocyte depression occurring at irregular intervals. However, detailed accounts of the hematologic findings were not presented, nor was the possibility of splenic neutropenia considered at that time. The case of chronic neutropenia reported by Hattersly,[4] which failed to respond to splenectomy, appears to be somewhat similar to our own although the presence of granulocytic hyperplasia of the marrow would tend to put it into a different category. Likewise, the five patients described by Adams and Witts[5] may also be of the same type. The first of these patients had chronic neutropenia unaffected by splenectomy but the others were assumed to be free of splenic effect because of the failure to find splenomegaly on physical examination. The bone marrows of this group varied widely between hypo- and hyperplasia. More recently an additional case of chronic neutropenia failing to respond to splenectomy has been reported by Armstrong.[23] The description of the bone marrow in this case is difficult to evaluate. The single cases of chronic neutropenia reported by Kopp[24] and Lawrence[25] would also seem to resemble the present syndrome, but again, adequate hematologic data are lacking. Bousser and Neyde[26] described a familial form of moderately severe chronic neutropenia in which this defect appeared to be transmitted as a mendelian dominant trait. These cases were characterized by an increased susceptibility to infections, especially of the throat, and hypoplasia of the granulocytic elements of the marrow. Splenomegaly was lacking and the course was prolonged and relatively benign. No evidence of familial or hereditary neutropenia was present in our cases. The cases of Cesar and co-workers[27] showed chronic neutropenia and a familial disposition, but albinism and congenital nystagmus were constant associated features which seem to relegate that group into a special category.

The available data permit little more than speculation as to the pathogenesis of the present neutropenic syndrome. No evidence of sequestration or excessive phagocytosis of granulocytes was seen either in the autopsied patients or in the spleens of the splenectomized patients. There was no evidence of nutritional deficiency or of bone marrow displacement. The defect seems to reside in a specific inability of the bone marrow to elaborate granulocytic precursors. Whether this defect is a congenital and genetic phenomenon, as in the cases described by Bousser and Neydé,[26] or whether it is the result of some acquired disorder acting upon the granulocytic precursors cannot be ascertained at present. Of some relevance may be the studies of Hickie[28] concerning the serum of a patient with chronic neutropenia and a bone marrow sparse in granulocytic precursors. This serum had the ability to render normal leukocytes unable to phagocytose bacteria of known susceptibility. Similar studies have been conducted by Furbetta and Buttaro.[29] Thus it is possible that a substance is present in the circulating blood which is noxious to mature leukocytes and which has, at the same time, the ability to inhibit the formation of their precursors. Adams and Witts[5] have suggested that this type of hypoplastic neutropenia may be a variant of the more generalized disease of the bone marrow, aplastic anemia. According to such a concept it would be analogous to the "pure red cell anemia" of Smith[30] in which there is a specific absence of erythrocyte precursors in the bone marrow.

Of interest is the remarkable paucity of symptoms sometimes shown by our patients even when they had a minimal number of circulating granulocytes. It is possible that the non-granulocytic leukocytes, particularly monocytes, have to some extent adopted functions normally performed by the polymorphonuclear series. In any event, monocytosis was almost constantly seen and in response to inflammation mononuclear infiltration appeared to replace the usual granulocytic form.

Providing infections can be controlled, the prognosis of the present syndrome is compatible with a lengthy course. This is evident from the persistence of the disease for at least twenty-seven years in one of our patients. The great strides in antibiotic therapy should further improve the outlook in other similar patients. Splenectomy has been of no value either in raising the white blood cell count or in altering the course of the disease and no response has occurred in the past with other methods of treatment. The possible effectiveness of the myelostimulatory action of ACTH and cortisone remains to be evaluated.

SUMMARY

Four cases of chronic neutropenia are reported which are non-splenic, non-cyclic and not related to any known disorder of leukopoiesis. Splenectomy performed in three of these patients failed to alter the course of the disease. The findings in all cases suggested the presence of a specific defect in granulocyte production by the bone marrow, possibly related to the aplastic anemias. It is suggested that these cases may fit into a syndrome best termed "primary hypoplastic neutropenia."

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Mediterranean Hemopathic Syndromes (Cooley's Anemia) in Adults*

Study of a Family with Unusual Complications

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COOLEY and Lee, writing in 1925,[1a] described a familial hemolytic anemia of infancy and childhood which soon became known to pediatricians and hematologists as Cooley's anemia. Three years afterward the senior author renounced the eponymic designation and called the disease "an erythroblastic anemia of childhood"[2a] because erythroblastosis was a prominent feature of the blood picture. Later, for reasons which will become apparent, he chose the term "Mediterranean anemia."[3]

The authors in their original presentation had studied seven cases of hemolytic anemia in infants and concluded that at least four of these represented a distinct disease unrelated to the group of anemias and splenomegalies which had been grouped under the name of von Jaksch's anemia.[4,5] All of their patients were children of Italian or Greek parentage. The disease began in infancy, as early as the third month of life. Prominent features in addition to stunting of growth were muddy pallor of skin and sclerae, icterus, hepatosplenomegaly, bone changes, and mongoloid facies manifested by high cheek bones, prominent eyes and epicanthic fold or shortened nose. The blood picture was striking. There was usually a marked hypochromic anemia, microcytosis and severe degrees of poikilocytosis. Target and oval cells were present in large numbers, and there were also polychromatophilia and basophilic stippling. A remarkable part of the hemogram was the presence in the peripheral blood of immature red cells in large numbers, especially erythroblasts and normoblasts. Moderate degrees of polymorphonuclear leukocytosis was present. In Cooley's cases the disease ran a fulminating course. It was resistant to all forms of therapy and death occurred in early childhood of anemia and intercurrent infection. Early students of the disease wrote that it was incompatible with life past the age of twelve years.[6b]

Subsequent developments, however, expanded the classical disease of Cooley with its relentless course and brief life span into a broader concept of inherited red blood cell diathesis of varying severity and duration. This brought the problem within the ken of clinical medicine in general. A rich literature rapidly grew up, especially in Italy and in the United States, as investigators studied hematologic, radiographic, pathologic and clinical aspects of the problem. The blood studies of Baty et al.,[7] Whipple and Bradford,[8] Wintrobe,[9] Dameshek[6b] and Smith[10a,b] verified and elaborated on the first observations of Cooley and Lee. They also pointed out for the first time that "formes frustes" might appear in older children or young adults who had mild forms of the disease or in elders who merely transmitted it. In this regard Caminopetros[11a,b] and Angelini[12] first noted that the most constant and at times only evidence of this state is increased resistance of the red cells to hypotonic saline solutions. Dameshek[6a,b] also reported this and it has become one of the most reliable diagnostic findings in the recognition of Cooley's anemia. Whereas the normal red cell is hemolysed at .35 per cent saline, the abnormal blood cells may be incompletely hemolysed in distilled water. There has been less unanimity concerning the role of the target cell, an abnormal erythrocyte with its hemoglobin content concentrated in the center and surrounded by an achromic area which extends to the periphery; since the central area is also elevated the cell has a Mexican hat appearance in profile. It was first identified by Haden and Evans[13] in

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sickle cell anemia and by Bywaters[14] and Smith[10d] in Cooley's disease. Dameshek[6b] suggested that the target cell might represent the fundamental defect in this syndrome, and the link between it and other inherited hemolytic anemias. However, Smith[10a] and Valentine and Neel[15a] take the position that the target cell is non-specific, and Barrett[16] showed that it appeared in a variety of conditions exclusive of blood disorders.

Studying the radiographic aspects of the bone changes, Caffey suggested that these are secondary to blood destruction and compensatory marrow hyperplasia.[17] This results in expansion of the medullary cavity at the expense of the cortex which is therefore abnormally thin. In time, compensatory changes appear in the presence of irregular trabeculations across the medullary cavity and the final stage may be one of sclerosis. X-ray may demonstrate involvement of any or all the bones, the most characteristic being in the distal end of the femur where a triangular expansion appears, in the skull with its perpendicular striations and in the hands where sclerotic bands intersect in the late stages and cause a mosaic pattern.

The bones and other viscera were studied postmortem by Whipple and Bradford.[8] In addition to the changes in the marrow and blood they discovered a characteristic deposition of pigment in the liver, kidney, pancreas, lymph glands, gastric mucosa, thyroid, adrenals and skin similar to that found in hemochromatosis. Little was found in the spleen. From their findings the authors concluded that the fundamental defect in the disease might be an abnormal capacity for utilizing iron and metabolizing hemoglobin.

However, the problem of pathogenesis is not yet resolved. Although jaundice and young red cell forms are indicative of increased hemolytic activity, it is unlikely that this is the only factor in operation since hemolytic crises do not occur.

Cooley[3] suggested that a primary disorder of the marrow with overstimulation and hyperplasia might be the critical factors. Yet, when the anemia is severe the marrow may show arrest of blood formation and the peripheral blood may be free of reticulocytes.[62] Attention has also been focused on abnormality of the red cell in this disease. Wintrobe[9] in 1940 predicated a fundamental defect in the erythrocyte, and Dameshek[6b] pointed out that although the fragility of the cell is decreased *in vitro* it may be increased *in vivo*. In a recent study Hamilton et al.[63] showed in one case that the survival period of the cells in Cooley's anemia is shorter than normal. It is evident that the problem requires further clarification.

Meanwhile, on a clinical and descriptive level investigators were organizing data into a comprehensive survey of the protean aspects of the disease. Wintrobe et al.,[9] Dameshek,[6b] Smith,[10a,c] Strauss et al.,[18] and Eliel and Bayles[19] in America, Silvestroni,[20a] Silvestroni and Bianco[20b] and Chini and Valeri[21] in Italy studied families whose members had varying degrees of hypochromic anemia or hypochromic polycythemia, target cells, icterus, splenomegaly and bone changes. The reports appeared in the literature under diverse designations: target-oval cell syndrome,[6b] familial hemopoietic disorder in Italian adolescents and adults,[9] familial microcytic anemia,[18] constitutional microcytic anemia[20] and Mediterranean hemopathic syndromes.[21] These reports were linked together by three fundamental elements: their nearly exclusive limitation to Mediterranean peoples, the presence of familial and hereditary elements, and the increased resistance of the red cells to hypotonic saline solutions.[21] Dameshek[6b] in 1943 first arranged the descriptions into a broad clinical and hematologic spectrum, ranging from the classical and lethal Cooley's disease on the one hand to isolated hematologic abnormality on the other. Whipple and Bradford[8] suggested the name "thalassemia," or anemia of the sea because of the predilection for peoples in the Mediterranean region. In a further effort at clarification, Valentine and Neal[15a] designated the severe condition as "thalassemia major" and the mild cases or trait as "thalassemia minor." Most of these titles have their disadvantages, including the name "erythroblastic anemia of childhood," suggested originally by Cooley, since it can be confused with the Rh factor disorder. Likewise "target and oval cell syndrome," and "familial" or "constitutional microcytic anemia" have no advantage of specificity. Finally even "thalassemia" or Mediterranean anemia does not take into account the reports of well documented cases in non-Mediterranean peoples of all races.[14,22–32] Moreover, the problem is further complicated by the question of the relationship of this entity to congenital hemolytic icterus,[33] sickle cell anemia,[6b,34,35] malaria[36] and the Rh factor.[37–39] In spite of this, however, the term "Mediter-

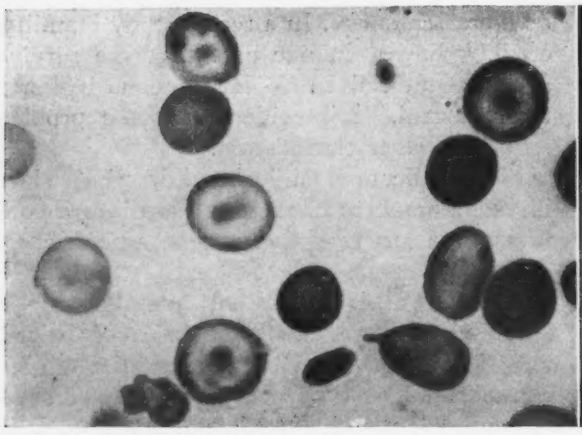

FIG. 1. A. DiR., peripheral smear showing a field of target cells with characteristic central accumulation of hemoglobin.

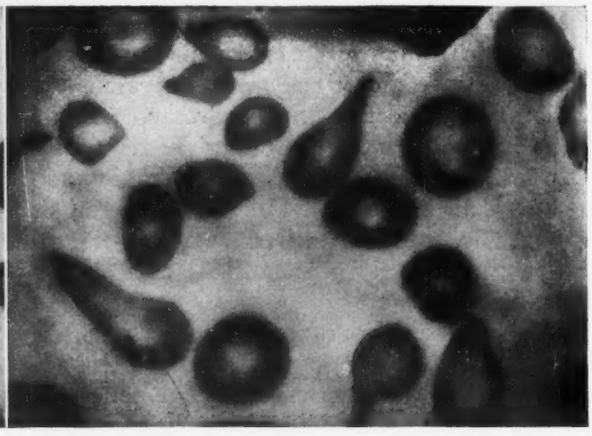

FIG. 2. A. DiR., peripheral smear showing marked anisocytosis, poikilocytosis, ovalocytosis and hypochromia.

ranean hemopathic syndromes," as suggested by Chini and Valeri[21] would appear to be among the most appropriate at this time.

Treatment of the severe form of the disease has been singularly unsuccessful. It is characteristically refractory to iron, to liver and vitamin concentrates, to endocrine extracts and blood transfusions. Splenectomy results in a spectacular increase in the number of nucleated red cells but there is no amelioration of the anemia. Radiation therapy is equally fruitless. Recent attempts have been made at treatment with exsanguinotransfusion,[37–39] nitrogen mustard[40] and metal-combining globulin.[41]

CASE REPORT

A. Di R., an Italian chauffeur aged thirty-four years, was admitted January 4, 1951. Ten days previously he had had sudden onset of severe substernal pain radiating to both arms and shoulders and to the neck, aggravated by effort and partially relieved by rest. It was associated with sweating and with rapid onset of dyspnea and orthopnea. In spite of symptomatic treatment his symptoms persisted and he became rapidly worse. A day prior to admission he experienced abdominal pain and distention.

He had been known to one of us since February, 1948, when he had complained of epigastric pain with pain-food-relief sequence. A gastrointestinal series disclosed an ulcer niche in the duodenum. At the same time there was marked enlargement of the liver and spleen on examination. Other findings included pallor, icterus and prominent cheekbones. Examination of the blood disclosed the hemoglobin to be 7.6 gm., and red blood cells 4,600,000. The white blood count was 21,150 and 15 to 20 nucleated red cells were present per hundred white cells. The smear likewise showed marked anisocytosis and poikilocytosis and hypochromia. The icteric index was 12, and the cephalin flocculation test four plus. His ulcer symptoms responded well to conventional medical management. The diagnosis of Cooley's anemia was established by further examination of the patient and his family. He worked steadily and was not seen again until the day of admission.

At this time the patient appeared acutely and chronically ill. He was orthopneic and sat rigidly because of abdominal pain and distention. The sclerae were icteric and pale. There was a peculiar yellow tint to the skin, and the facies was noted to be somewhat mongoloid. The skin was warm and moist, and there was distention of the cervical neck veins. Both bases were flat; tactile fremitus and breath sounds were absent. Fine rales were heard in both interscapular areas, but the apices were clear. The area of cardiac dullness extended into the flatness of the lung fields. The rate was 130, regular. There was a loud to-and-fro friction rub at the left sternal border and a questionable systolic murmur at the apex. Blood pressure was 140/60. Over the left lower thoracic cage and upper abdomen there was a large area of hyperpigmentation. The epigastrium was distended and tympanitic. The spleen extended to the crest of the ileum and the notch was felt at the level of the umbilicus. The liver was 3 or 4 cm. below the right costal margin, hard and

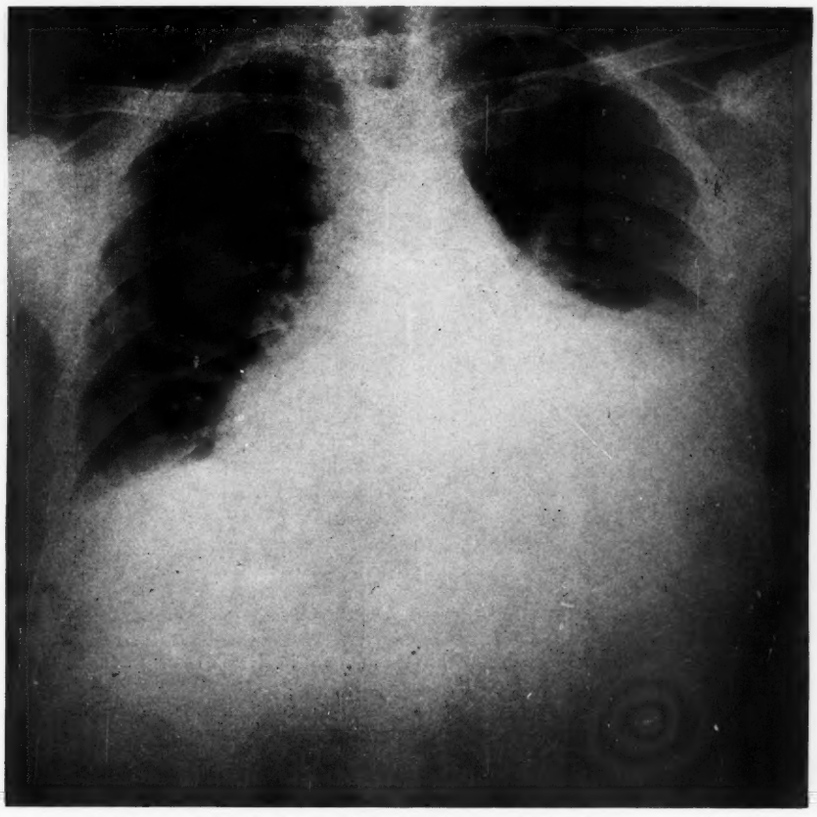

FIG. 3. A. DiR., admission chest plate showing marked enlargement of the heart and bilateral hydrothorax.

non-tender. There was no peripheral edema. Rectal and neurologic examinations were non-contributory.

Laboratory data were as follows: hemoglobin 5.3 gm., red blood cells 2,780,000, white blood cells 12,000 with 89 per cent polymorphonuclears. The smear contained 12 nucleated red cells per 100 white cells. There were many target cells (Fig. 1), stippled red cells, polychromatophilia, anisocytosis and poikilocytosis. (Fig. 2.) Hemolysis began at .36 per cent saline and was incomplete in distilled water. The urine contained a trace of albumin, a few white cells and occasional pus cells. ESR, 10; NPN, 40 mg. per cent; blood sugar, 122 mg. per cent; total protein, 7.0 gm. per cent; albumin, 3.3 gm. per cent; globulin, 3.7 gm. per cent; uric acid, 7.3 mg. per cent; phosphorus, 3.8 mg. per cent; alkaline phosphatase, 4.2 Bodansky units; total cholesterol, 56 mg. per cent; free cholesterol, 40 mg. per cent; bilirubin, 3.0 mg. per cent. The blood culture was sterile. Sputum culture was positive for Staph. aureus and hemolytic streptococci. X-ray of the chest disclosed enormous enlargement of the heart and bilateral hydrothorax, more marked on the left. (Fig. 3.) The electrocardiogram showed inversion of the T wave in V_2 and slight elevation of the S-T segment. The P-R interval was .16 and no other abnormalities were noted.

The patient had a fever of 102.6°F. on admission and it reached 103.8°F. on the third hospital day. Repeated blood culture was sterile. When the patient failed to respond to antibiotics, cortisone was administered, 300 mg. on the first day, 150 mg. for the four succeeding days and then 100 mg. daily. A pleural tap was done and 450 cc. amber fluid was withdrawn from the left pleural cavity. The specific gravity was 1.017 and the fluid contained moderate leukocytes and monocytes. Culture for microorganisms including tubercle bacilli was sterile. On the fourth day of treatment the patient's temperature was 100°F. and there was no further elevation in this period of his hospital stay. There was a concomitant drop in pulse rate and the patient appeared much improved. On the seventh day of treatment the friction rub was not heard and a soft systolic murmur was audible. There was no reaccumulation of

FIG. 4. A. DiR., skull film showing expanded medullary cavity and perpendicular striations. The outer table is markedly attenuated.

pleural fluid. Reexamination of the chest radiographically demonstrated a diminution in the size of the cardiac silhouette and clearing of the lung fields. Cortisone was discontinued on the fifteenth day.

The anemia was treated by blood transfusions but the hemoglobin did not exceed 10.0 gm. The stools were positive for occult blood and a gastrointestinal series confirmed the previous diagnosis of duodenal ulcer. A bone survey demonstrated widening of the cranial vault with perpendicular striations across the medullary cavity (Fig. 4), flattening and osteoporosis of the vertebral bodies and expansion of the medullary cavities of the long bodies. Flat plate of the abdomen showed calcification in the left splenorenal region and characteristic striations in the pelvic bones. Retrograde pyelography indicated that the calcification was outside of the urinary tract. No dye was recovered from the ureter on the left side and the kidney was thought to be non-functioning.

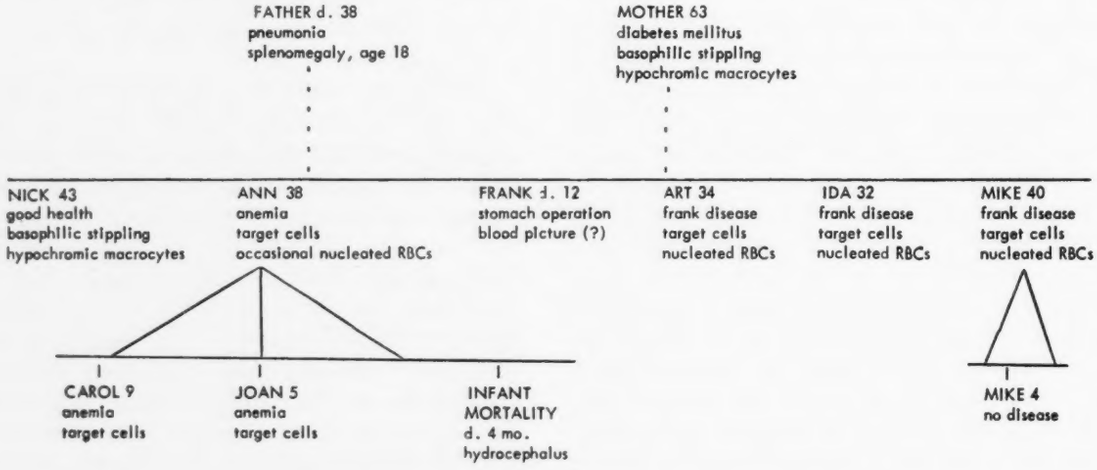

FIG. 5.

Agglutination tests for streptococci, viral disease, typhoid and paratyphoid fevers, brucella, proteus OX19 and the heterophile antibody remained within normal limits. The tuberculin reaction was negative.

On two occasions there was an acute inflam-

matory process at the metatarsophalangeal joint of the left great toe. The joint was swollen and the overlying skin was dusky and erythematous. There was great tenderness on lateral pressure. The uric acid was 7.7 mg. per cent. Salicylates did not affect the lesion but there was dramatic relief with colchicine. Radiographic examination of the joint was normal. The patient was discharged during the tenth hospital week.

Seen in the follow-up clinic five months later, he was working steadily as a chauffeur. He said that he had been well except for a temporary recurrence of ulcer symptoms following dietary indiscretion.

The patient is one of a family of six siblings. The father and mother are both Italian and were born in the province of Potenza not far from Naples. The mother is in good health at the age of sixty-three with the exception of mild diabetes. Her hemoglobin is 12.4 gm., red blood cells 4,800,000, white blood cells 10,500 and the differential count is normal. However, the blood smear is loaded with red cells showing basophilic stippling and there are many hypochromic macrocytes. These are the usual blood findings in mild forms of Cooley's disease.[10b]

The father died at the age of thirty-eight of pneumonia. He is known to have had splenomegaly since the age of eighteen and was thought to have malaria. Since both diseases are common and coexist in the same regions of Italy, it was not unusual for misdiagnoses to be made.[42] His brother is said to be in good health. However, one of the latter's five children is known to have died of Cooley's anemia at the age of twenty-eight. The other children are said to be free of the disease. We have not been able to examine this branch of the family.

Figure 5 is a representation of the patient's immediate family. At the time of the father's death when the patient was three years old, and his brother Mike was aged nine, they were examined by a welfare board physician and splenomegaly was noted. Both had irradiation of the splenic area.

Mike, now aged forty years, has mongolian facies, icteric skin and hepatosplenomegaly. His hemoglobin is 8.7 gm., red blood count 3,430,000, white blood count 12,000. The smear has anisocytosis, poikilocytosis, moderate achromia and frequent nucleated red cells. Blood chemistry examination: NPN, 28 mg. per cent; uric acid, 8.3 mg. per cent; calcium, 10.5 mg. per cent; phosphorus, 3.2 mg. per cent; alkaline phosphatase, 3.3 Bodansky units, bilirubin, 3.2 mg. per cent. Radiographic examination of the bones showed the typical changes of Cooley's anemia. (Fig. 6.) The flat plate demonstrated calcification in the right upper quadrant proven by intravenous pyelogram to be extrarenal (cf. Ida). Mike has a twelve year old son who has no clinical or hematologic evidence of disease.

FIG. 6. M. DiR., x-ray of elbows with striations resulting in "honey-combed" appearance around elbow joint.[10c]

Ida, now thirty-two years old, has been followed by one of us since June, 1939. She had developed an ulcer over the right medial malleolus after kicking a football. The ulceration was persistent, had a necrotic base and an indolent zone of granulation tissue. On examination the patient was icteric and had high cheek bones. A hard spleen edge was felt well below the left costal margin. The hemoglobin was 7.5 gm., the red blood count 3,020,000 and the white blood count 6,600. The smear showed target cells, hypochromia and marked poikilocytosis. There were eight nucleated red cells per hundred white cells. The urine was positive for bile. The ulcer was treated with cod liver oil compound, gentian violet and mercurochrome dressings. In addition the patient received iron, liver injections and a high caloric diet. In spite of these measures the ulcer failed to heal and a new one appeared over the left medial malleo-

FIG. 7. I. DiR., showing large serpiginous ulcers over both medial malleoli. The lateral malleolus of the right ankle is also involved.

lus. She was admitted to the hospital in August, 1944. Large serpiginous ulcers were seen over both malleoli of the right ankle and over the medial malleolus of the left. (Fig. 7.) The floor of the ulcers was greenish and there was a foul odor. The edges were rolled under and slightly elevated. The spleen was at the umbilicus and the liver was two fingers below the right costal margin. The sclerae were icteric. There was no abnormality of the heart or lungs. The hemoglobin was 6.4, red blood count 2,950,000, white blood count 8,000 with a normal differential count. There was achromia, microcytosis, anisocytosis, poikilocytosis, target cells and stippled red cells. Blood chemistry: NPN, 26 mg. per cent; total protein, 7.5 gm. per cent; albumin, 4.4 gm. per cent; globulin, 3.1 gm. per cent; cholesterol, 71 mg. per cent; cholesterol esters, 41 mg. per cent; bilirubin, 3.8 mg. per cent. Changes in the skull, vertebrae and pelvis were again characteristic of Cooley's anemia. The ulcers improved temporarily on potassium permanganate and tyrothricin dressings but soon reappeared and have remained.

In 1949 the patient complained of pain in the right loin and passed brown stones in her urine. The sediment contained 250 red cells per high power field. There were no crystals. Retrograde pyelograms demonstrated a staghorn calculus in the right kidney pelvis, and calcification in the lower pole of the left pelvis. (Fig. 8.) Reexamination in April, 1951, following suprapubic pain and hematuria disclosed a large calculus in the left renal pelvis. X-ray spectroscopic examination of the small stones removed during cystoscopy indicate that they are composed of uric acid, calcium urate and ammonium acid urate. The uric acid in this period was 12.0 mg. per cent; NPN, 49 mg. per cent; cholesterol, 80 mg. per cent; free cholesterol, 35 mg. per cent; bilirubin, 1.1 mg. per cent; calcium, 8.5 mg. per cent; inorganic phosphorus, 4.9 mg. per cent and alkaline phosphatase, 2.5 Bodansky units. In spite of chronic renal disease the patient carries on her activities as a housewife and is symptom-free in the intervals between passage of renal calculi.

Ann is now thirty-eight years old. She has been under observation since 1940. In 1938 she gave birth to a baby who died at four months of hydrocephalus and other congenital anomalies. When first seen by us her hemoglobin was 76 per cent and red blood count 3,940,000. The Cooley trait was diagnosed by the presence of numerous target cells, anisocytosis and poikilocytosis. She was treated with large doses of iron and liver and gave birth to Carol, nine, and Joan, six. Both girls show a hypochromic polycythemia, and their blood picture is consistent with the Cooley trait. Their mother likewise has a hypochromic polycythemia at this writing.

Of the two remaining siblings, Nick, forty-three, is in excellent health but has blood changes similar to the mother's. Frank died at the age of twelve, following a surgical procedure. He had none of the gross stigmata but there is

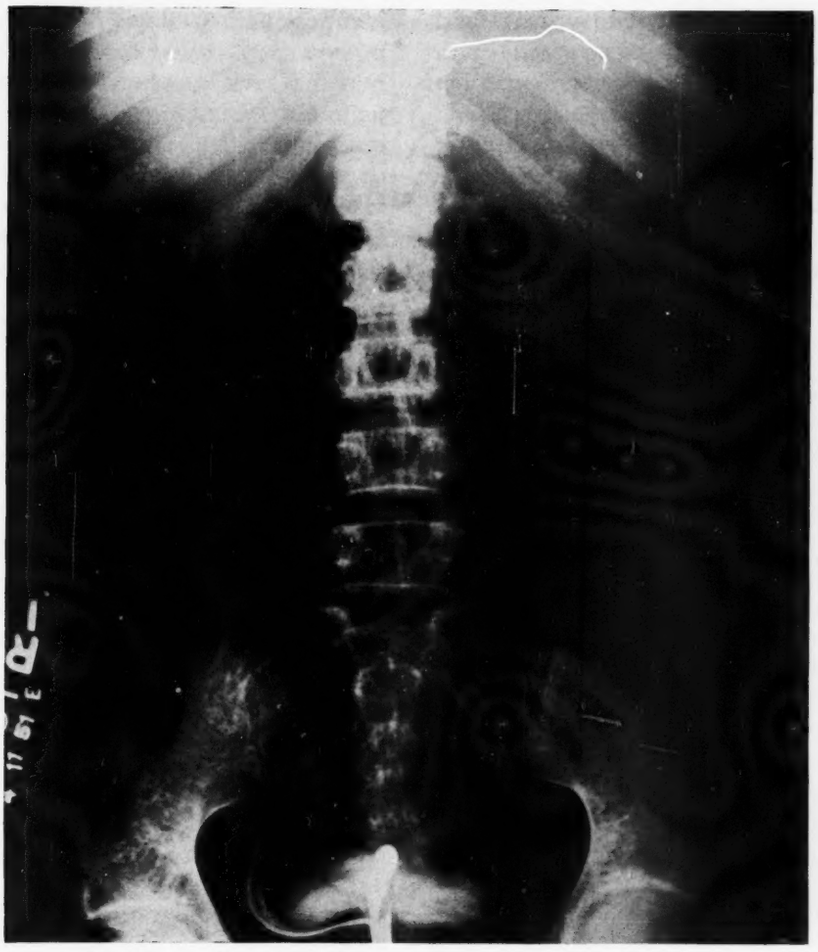

FIG. 8. Flat plate of lumbar spine and sacrum showing osteoporosis and coarse compensatory striations. A large staghorn calculus is seen in the left kidney pelvis.

no information available about his blood picture.

COMMENTS

The development of the literature on Cooley's anemia has been briefly traced. Our cases, reviewed in relation to these developments, offer some notable features and it is to these singular aspects that attention is now drawn.

The disease is not the rarity it was once thought to be. Neel and Valentine in a statistical survey of Rochester, a city with a large Italian population, estimated that it occurred in the severe and lethal form once in 2,368 births.[43] Smith, with an extensive experience in New York City and surrounding areas, found that area to be a large reservoir for the disease because of the immigration from Italy in the late nineteenth and early twentieth centuries.[10b] The incidence of the trait or mild form must be widespread. In the Rochester survey[43] it was 1 in 125 births, calculated on the assumption that the mechanism of inheritance is recessive.

Nevertheless the presence of full-blown Cooley's disease in the fourth and fifth decade of life is not frequent. Dameshek reported his celebrated Caruso case in 1940, a twenty year old boy with anemia, splenomegaly and bone changes.[6a,b] Wintrobe, in the same year, reported an eighteen year old boy with jaundice, splenomegaly and anemia but no bone involvement.[9] The parents and siblings had the mild disease, represented either by splenomegaly, anemia or increased erythrocyte resistance. He reviewed the literature and found seven cases over fourteen years of age. He cited Mandeville's fifteen year old boy with bone changes,[44] Dalla Volta's thirty year old patient with autopsy findings as described by Whipple and Bradford,[45] the three cases of Aravantinos and Delijannis, aged six-

teen, twenty-one and twenty-two years,[46] and the twenty-four year old pharmacist with jaundice and splenomegaly described by Allen and Childs.[47] Wolman and Dickstein in 1946[5] referred to the two adults of Caminopetros,[11a] the fourteen year old boy of Thalheimer,[49] the nineteen year old boy of Smith,[10c] the seventeen and twenty year old siblings of Atkinson,[50] the thirty-nine year old patient of Eliel and Bayles with characteristic blood and spleen,[51] Fawdry's six adult cases[52] and the patients of Van Ravenswaay,[42] Voorhies and Sloan.[53] We are adding the two adult cases of Thomopoulu.[48] In a further review of these cases Chini and Valeri[21] reiterate the popular distinction between the "severe" and "mild" forms, the "thalassemia major" and "thalassemia minor" of Valentine and Neel.[15a] The severe form is designated as the classic case of Cooley, developing exclusively in children and going on to fatal termination with intense anemia, splenomegaly, erythroblastic hyperplasia and bone changes. The mild form, which runs a less rapid course, allows patients to reach adult age. It is in the latter category that they would group the adult cases enumerated above to which they add reports from the Italian literature. However, these authors acknowledge that in the "minor" classification according to this scheme there might be included well defined syndromes some of which are of marked severity, and for which the term "minor" would hardly be acceptable.

Our own cases are in the fourth and fifth decade of life. Ida is thirty-two, Art thirty-four and Mike is forty. Each of them appears to have the mongoloid facies, the muddy pallor and icteric sclerae so characteristic of patients with this disease. The blood pictures were typical in each case. Our patients had microcytic anemia of varying severity, and the hemoglobin ranged from 4.8 for Arthur to 6.4 for Ida, and 8.7 for Mike. The smears showed the anisocytosis, poikilocytosis and target cells so often described, and in addition all showed nucleated red cells in the peripheral blood. Art's blood cells showed markedly increased resistance and were not completely hemolysed in distilled water.

In each instance hepatosplenomegaly was present. These viscera were hard, smooth and non-tender. In Ida the spleen extended to the umbilicus and in Arthur and Mike to the iliac crest. Likewise, widely disseminated bone changes were evident on radiographic examination of each of the three siblings and these were identical with Caffey's description.[17] The basic process was osteoporosis, expansion of the marrow cavity, cortical attenuation and compensatory striation. In the skull the "hair-on-end" appearance was seen; in the distal end of the tibia expansion of the medullary structure resulted in a flask-shaped appearance; in the hands, vertebrae and sacrum interlacing bands of varying density produced a mosaic pattern. From the clinical, hematologic and radiologic data it is clear that these cases fall at the "severe" end of the Cooley spectrum, and the term "mild" or "minor" is hardly warranted.

Two of the three siblings who have the complete Cooley diathesis developed clinically significant complications, and all three had hyperuricemia. Arthur was admitted with severe pleuropericarditis. On x-ray there was a markedly enlarged cardiac silhouette and bilateral pleural effusion. The history did not suggest rheumatic fever, and tuberculosis, uremia and coronary disease were soon excluded. He was considered too ill to warrant a diagnosis of non-specific pericarditis although there has been a report in the recent literature of a fatality in this benign disease.[54] The spectacular response to cortisone was of little diagnostic value since this hormone is known to act non-specifically in a large group of diseases. It could not be definitely established that this was a direct complication of the Cooley syndrome although the literature is not without precedent for this. Cooley et al.[1a,b] in their original cases describe two siblings of eleven months and three and one-half years, respectively. One of these developed a pericardial effusion in the course of the disease, and another had terminal edema and cardiac dilatation. Whipple and Bradford[8] mention the presence of fluid in the serous cavities. One of their cases had edema with pericardial and peritoneal effusions developing in the later months of life. Wintrobe in his textbook mentions the presence of fluid in the serous cavities.[55] However, this complication was not previously reported in the adult cases.

Leg ulcers in Cooley's disease have been described once previously in the literature. Estes, Farber and Stickney[56] treated three sisters of Italian descent aged thirty, twenty-three and nineteen years, respectively. The ulcers characteristically appeared over the malleoli, healed slowly and with scarring, and recurred. In our patient, Ida, the ulcers ap-

peared on the right leg in 1939 and over the left leg in 1944. They were large, serpiginous and had rolled edges. No complicating vascular disease was present. In contrast to Estes' cases the ulcers in our patient had little tendency to heal although a large variety of therapeutic agents were employed. In sickle cell anemia, in which leg ulcers are common, the cause is said to be clumping of abnormal red blood cells. Whether a similar pathogenesis exists here and whether Arthur's duodenal ulcer is part of the same process is not clear.

Hyperuricemia was constant in all our cases and ranged from 7.7 mg. per cent in Arthur to 12.0 mg. per cent in Ida. Although Mike with a uric acid of 8.3 mg. per cent had no complications, this was not the case with the other two siblings. Ida has bilateral renal lithiasis, and the calculi were composed of calcium and ammonium acid urates. Pain and infection were clinical problems on a number of occasions. The serum calcium and alkaline phosphatase values were normal. There was no crystalluria either on immediate examination of a voided specimen or on examination after twenty-four hours, but albumin, red cells and pus cells were constantly present. In Arthur the corollary of hyperuricemia was two episodes of acute gouty arthritis. There was on each occasion involvement of the left first metatarsophalangeal joint. There was dusky erythema and extreme tenderness, receding rapidly with colchicine. Hyperuricemia and gout may complicate pernicious anemia in a period of remission following liver therapy. In our patient the event could not be correlated with a hematologic crisis.

Mike showed on flat plate of the abdomen a calcified area in the right upper quadrant, proven to be extrarenal by intravenous pyelogram and suggestive of a biliary calculus. There is a recent report in which thirty-five bilirubin stones were removed from the gallbladder of a twenty-one year old Italian girl with thalassemia.[61] There had been no previous reports of this in the literature.

The final point of interest in the discussion of our material is the question of genetics. Perhaps the most widely accepted theory of inheritance of Mediterranean hematologic syndromes is that first offered by Caminopetros,[11] and now accepted by many investigators in Italy and America.[6b,15a,58,59] This view, as expressed by Valentine and Neel, is that "thalassemia is owing to homozygosity for a factor which when heterozygos produces the mild anemia, i.e., the factor responsible for thalassemia is either an incomplete recessive or a semidominant. Otherwise stated, full-blown thalassemia is inherited as a recessive characteristic but the heterozygote as well shows significant changes in the blood."[15a] Cooley[2b] and Smith[10a,b] believe the disease to be inherited by a single dominant gene variably expressed, although the latter in an analysis of forty-seven families concluded "that in every family with a severely anemic child both parents have the trait for the disease."[10b] Finally, McIntosh and Ward[57] suggested that the mechanism of inheritance is through the simultaneous presence of two nonallelomorphic dominant factors, one inherited from each parent.

Our experience, then, is in accord with the popular view on the mode of inheritance. The mother has blood changes typical of the "mild" or "carrier" form of the disease. The father with a history of splenomegaly discovered in early youth very likely had Mediterranean disease, too. It would appear that the "severe" disease was inherited through both parents and that these children are homozygous whereas the children who are asymptomatic but who have blood changes are heterozygous.

CONCLUSIONS

It is no longer tenable to regard the "severe" form of Cooley's disease with homozygous inheritance as being invariably lethal in infancy and childhood. From the literature and from the case reports we have presented it is seen that patients with all of the well known stigmata may live to the fourth and fifth decades. They may fare well and be gainfully employed in spite of their apparent susceptibility to diverse complications: renal calculi, leg ulcers, gouty episodes, peptic ulcer, cholelithiasis and cardiac disease.

The classical description of Cooley is one aspect of a disease with widespread and protean manifestations. The multitudinous names and subdesignations under which this disorder has appeared in the literature are in large part a consequence of this, and it has resulted in much confusion and duplication of effort. Dameshek was the first to suggest that several hematologic disorders related to the disease described by Cooley had been reported separately, and that they could be grouped together in spectral fashion from most mild to most severe. Indeed,

it would seem in keeping with the facts at hand to employ a broad term like "Mediterranean hemopathic syndromes"[21] to include those disorders which (1) have a predilection for Mediterranean peoples, (2) have a familial incidence and (3) which have decreased red blood cell fragility, and/or certain hematologic abnormalities as a constant finding.

SUMMARY

1. Cooley's anemia in three siblings in the fourth and fifth decades of life is reported. All criteria for the severe form of the disease were present, and these cases appear to be among the most striking described in middle-aged adults.

2. Complicating features of the disease were reported and they include leg ulcers and hyperuricemia which in one patient resulted in urate calculi and in another expressed itself as gouty arthritis.

3. Pleuropericarditis which responded to cortisone is described in one of the patients and its relationship to the basic disease is discussed.

4. The literature on Cooley's anemia is reviewed, and the protean forms of disease outlined, along with the numerous designations and subdesignations under which they have appeared in reports. The possible mechanisms of inheritance are mentioned.

5. A broad designation such as "Mediterranean hemopathic syndromes," as suggested by Chini and Valeri would seem more suitable than the other terminologies which have appeared in the literature, since the latter do not adequately express the remarkable clinical and pathologic variations of the disease.

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Review

Circulating Blood Eosinophils in Acute Infectious Disease and the Eosinopenic Response*

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The recent revival of interest in the eosinophil cell has been due chiefly to its usefulness as an indicator of adrenocortical activity. This interest has extended into the more fundamental and still unsolved problem of the nature and function of the eosinophil cell. Review of a massive accumulation of factual data is now in progress in many laboratories. It seemed, therefore, worth while to re-examine a single facet of this larger problem, the natural behavior of this cell in the blood in acute infectious disease.

A brief historical review of the significance of the eosinophil cell may well begin with Wharton Jones'[1] description in 1846 of a coarsely granular stage of the blood corpuscle. No significant progress was made until Ehrlich[2] in 1878–79, on the basis of his differential staining, clearly separated the leukocytes into distinct types. Quickly many studies on these cells followed, stimulated chiefly at first by Ehrlich and his pupils. The eosinophil shared in this activity and by 1893 when Zappert[3] published the first extensive review, the broad outline of our current basic information had already been established. The general surveys of the eosinophil cell published in this country by Brown[4] in 1903 and Simon[5] in 1906 are still largely valid today. Details, however, continued to be added, and by 1914 Schwarz[6] in his monumental monograph discussed the subject under three major sections (the eosinophil leukocyte, blood eosinophilia and tissue eosinophilia) and was able to accumulate 2,758 references. Interest was sporadic after this, until recently. Rud's[7] monograph is an excellent summary.

Out of a welter of many facts and theories only limited conclusions were reached: (1) The eosinophil is a cell *sui generis* derived from a stem cell in the bone marrow;[8,9] (2) the blood and tissue forms are probably identical[9,10] and (3) the eosinophil is in some way related to the protein molecule and immune processes.[7,9,11] Its mode of action and its control remained completely elusive. Control of its action by the autonomic nervous system was postulated early but this theory did not progress beyond inconclusive scholasticism.[6,7]

Since an increase in the number of eosinophils in the blood was technically easier to study than a decrease, clinical data on eosinophilia grew rapidly. It was established quite early that eosinophilia occurred fairly uniformly in many allergic conditions, in a variety of generalized dermatoses and in parasitic infestations. It occurred frequently in postinfectious and post-toxic conditions, in certain infections, especially in their chronic forms, in many blood dyscrasias, in malignancies and as a reaction to many drugs. It was found also in a heterogeneous collection of unrelated conditions.[12,13]

Eosinopenia, on the other hand, although noted by Ehrlich[14] in 1880, has been emphasized infrequently or completely neglected until recently. Naegeli's textbook[15] lists its occurrence in acute infectious disease, intoxications, following major surgery, pernicious anemia and vaguely defined endocrine disturbances.

In acute infectious disease the role of a fall in circulating blood eosinophils has been most noticeably stressed. That an eosinopenia occurs in acute infections was first noted by Ehrlich[14]

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in 1880. Canon[16] in 1892 studied the blood eosinophils in a group of varied illnesses, including typhoid, malaria, severe influenza and septicemia. In all the blood eosinophils were either reduced or absent. Of seven patients with septicemia only two recovered and these two had the largest number of eosinophils in the blood. Canon pointed out further that the reduction in the number of eosinophils was an absolute not a relative one.

Zappert[17] in his first report in 1892 commented briefly on the absence of eosinophils at the height of the fever in a series of febrile illnesses, namely, pneumonia, typhoid, sore throat and puerperal sepsis. In the following year he[3] discussed in detail the eosinophil cell reduction in pneumonia, typhoid, septicemia, erysipelas, malaria, acute rheumatism, acute exanthems and febrile tuberculosis. He considered postinfectious eosinophilia a favorable sign and noted a further reduction during the agonal period.

Türk in his monograph[18] in 1898 summarized all previous work which he corroborated in his own study of fifty-two cases as follows: pneumonia eighteen, acute rheumatism eight, typhoid five, malaria four, acute meningitis three, measles three, tuberculosis two, septicemia two, scarlet fever two and mumps one.

Subsequently, studies on specific diseases, chiefly but not always corroborative of the earlier ones, appeared in fair abundance although in recent years only occasionally. The following list is representative: appendicitis,[5] atypical pneumonia,[19] cholera,[20] dengue,[21] diphtheria,[15,22,23] erysipelas,[3,18] exanthum subitum,[23] infectious mononucleosis,[23–25] influenza,[15,16,26] malaria,[3,15,16,18] measles,[18,22,23,26,27] meningitis,[18,28] mumps,[18,23] pneumonia,[3,15,18,26,29,30–33] rheumatic fever,[34] rubella,[23] scarlet fever,[15,18,22,23,35,36] trichinosis,[15,37–39] typhoid fever,[3,15,16,18,26,40–43] typhus,[44] varicella[15,23,45] and variola.[15,26,46]

Even though the emphasis varied, most observers reached the same limited conclusions, namely, the eosinophil cell count of the blood falls, even to complete disappearance, in acute infectious disease. The degree of the fall is roughly a function of the severity of the illness. Conversely, there is usually a postinfectious eosinophilia. Both the eosinopenia and eosinophilia are useful prognostic signs. The latter achieved greater emphasis and several terms such as dawn of cure,[12] index of convalescence[47] and dawn of convalescence[48] were invented.

Analysis of this body of data on the eosinophil response in infectious disease reveals that the obvious non-specificity of the reaction was only passively acknowledged or wholly ignored, and that with few exceptions[49,50] the eosinophil response was studied and interpreted in relation to each specific disease. An excellent illustration is Naegeli's[40] dictum in 1900 "dass eine Krankheit niemals Typhus sein kann, bei der die Eosinophilen halbwegs normaler, normaler (100–200) oder gesteigerter Zahl vorkommen," which was quoted repeatedly in the literature[51] and appears in two recent American textbooks.[52,53]

This specific approach was responsible also for a considerable literature on the value of eosinophilia as a diagnostic and prognostic sign[23,36] in scarlet fever, a disease in which eosinophilia appears relatively early in its course. It had, of course, been noted by many of the same investigators[23,35,36] that the eosinophils in scarlet fever are normal, depressed or absent during the first two to three days of the illness, and absent in fatal cases.

In trichiniasis in which eosinophilia is of great diagnostic importance the recent literature seems largely to ignore the fact that during the early course of the disease or in severe cases the eosinophils are reduced or absent, even though this was noted as long ago as 1889 in humans by Howard[37] and in 1904 by Opie[38] in experimental trichiniasis in guinea pigs. Naegeli[15] ascribed the rapid fall or disappearance of the eosinophils in fatal cases to bone marrow insufficiency.

In a recent article Kauffman[25] concluded that eosinophilia is of diagnostic significance in infectious mononucleosis. There seems to be no awareness in this work of the non-specific nature of the eosinophilia and he dismisses lightly the finding by others[24] of an eosinopenia in the early stages of the disease.

Such a specific and now classic approach to the behavior of the eosinophil in the blood in acute infections has been fully adopted and elaborated in many textbooks and monographs.[6,7,15,51,54] It is, therefore, difficult to understand how in recent years the eosinopenic response in infectious disease has been either ignored or unknown, especially in this country. Articles on specific infectious diseases, with few exceptions,[33,34] have discussed eosinopenia briefly[32,55] or not at all,[45] or apparently as a newly described finding.[41–43,56] Several recent review articles[9,57–60] on related subjects barely

mention eosinopenia. In a number of the more current textbooks several mention it only casually[52,53,61–64] while others ignore it entirely.[65–67] In one textbook[61] there occurs only the following statement, "Their (eosinophils) absence is of little importance but their increase is often of great help in diagnosis."

A restudy of this problem is evidently indicated. By way of beginning, it was decided to study the patients admitted to this hospital with ordinary infectious diseases and analyze them for possible simple clinical correlations. Elaborate metabolic and endocrinologic studies are obviously necessary but were not attempted in this study.

METHODS AND MATERIAL

Twenty-six patients were studied on the Infectious Disease ward of this hospital. There was no selection of material other than the presence of an acute infectious episode, either primary or superimposed on a chronic illness.

Patients were fasted overnight. Venous blood was generally drawn into oxalated bottles before 9 A.M. and sent to the routine laboratory for all tests except the eosinophil count. A part of the blood sample was retained and, using a Levy counting chamber of 0.2 mm. cell depth, an eosinophil count was done usually within a few hours by the method of Randolph.[68–70] In several instances the retained portion of the blood specimen was kept at room temperature or in the refrigerator and repeat counts were done as late as twenty-four hours after drawing the blood. The counts showed surprising uniformity within the limits of technical error and confirmed the fact that the eosinophil is the hardiest of the blood granulocytes[7,54,71–73] and may live for ten to fourteen days.[72] Usually, eosinophil counts were made daily and by the same individual in each patient. In a few patients several counts were made during the same day or night.

The normal values for the blood eosinophil count, as reported in the literature, show great divergence, both in maximum and minimum values (50 to 500 per cu.mm.) and in the mean value.[7] For use in the diagram 200 per cu.mm. has been adopted as the most commonly accepted normal value.[62] In individual patients this may be too high or too low and this must be kept in mind in the interpretation of the diagrams. To minimize such errors the eosinophil counts were continued, whenever feasible, until the values were reasonably stable. The diurnal variation in the normal count[7,49,74,75] was avoided by standardization of the time of each count as described before. The danger of using single determinations for comparison[7,75] was not discounted; interpretation was based on trends in the curve rather than on single values.

ANALYSIS OF CLINICAL DATA

Age and Sex. The twenty-six patients were typical of the average Veterans' Hospital population, twenty-four males, of which two were Negro and two females. Fourteen of the patients were in the third decade of life, six in the fourth, one in the fifth, two in the sixth and three in the seventh.

Fever. In general, the higher the temperature the more profound was the drop in the eosinophil count. Cases I, II, VII and XV showed a total absence of eosinophils during the height of the fever. On the other hand, Case V also showed a total absence when the temperature was less than 102°F. and Case IV at a time when the temperature reached 103.6°F. showed 62 eosinophils/cu. mm.; in Case VI when the temperature reached 106°F. the eosinophils varied from 56 to 94/cu. mm. and in Case XIV a temperature of 104.5°F. was accompanied with an eosinophil count of 94/cu. mm.

That the fever *per se* is not responsible for the eosinopenia can be seen in Cases I, III, IV, VI and IX in which the eosinophils rose to normal or higher levels before subsidence of the fever.

Leukocytes. Although in several cases, e.g., II, V and VII, the eosinophil count was low when the total leukocyte count was high and the polymorphonuclear percentage was increased, in general a consistent correlation of leukocytosis and eosinopenia was not evident. Even the presence of total leukocyte and polymorphonuclear counts in the normal range, as in Cases VI, X and XI, did not seem to interfere with the eosinopenic reaction.

Erythrocyte Sedimentation Rate. No consistent correlation was discernible in any direction.

Clinical Status. The clinical appearance and severity of symptoms seemed to offer the best correlation with the eosinopenia. For instance, in Cases I, II, V, VI and VII symptoms were at their height when the eosinophils were absent or sharply reduced. However, the relationship was difficult to quantitate and the degree of the eosinophil reaction seemed to vary with the individual, possibly with his own normal base

line. In many cases the eosinophils rose to normal or much higher levels even while the patients were still sick (Cases I, III and IV). In a few patients the eosinopenia persisted for varying periods even after symptoms had disappeared (Cases V, VII and X). It is of interest to note that the eosinophils did not seem to fluctuate with the extent or continuation of physical signs and the pathologic process.

The length of time during which the eosinopenia persisted was unpredictable. For instance, in Case VII the low eosinophil count was present for more than three weeks even though the patient became asymptomatic much earlier. Similarly, the postinfectious rise was variable in relation to the time of its appearance, its extent and its duration. The highest values were obtained in Cases I, II and III. Case I was uncomfortable but not toxic; yet the eosinophilia persisted for more than a week. In Case II, a critically ill patient, it rose and fell sharply in a few days.

Chronic illness did not seem to interfere with the eosinopenic response. Case VIII, a patient with severe Parkinsonism; Case XI, with severe bronchial asthma; Case XII, with general debilitation; and Case XIV, with bronchogenic carcinoma—all reacted promptly to the acute infectious episode.

Antibiotics did not appear to exert any influence on the eosinophil count. If they improved the clinical status of the patient, the previously described changes were noted.

Case XXVI was included in this series since the patient was originally referred with the diagnosis of influenza, but more especially because it illustrates the dissociation of the eosinopenia and pathologic findings. The eosinophil count rose even though the patient died several days later and showed extensive myocardial necrosis. (Figs. 1 to 26.)

COMMENTS

In general, our results are in agreement with those published by others. The good correlation of the eosinopenia with certain clinical aspects in a variety of infectious diseases and its failure to correlate as consistently with the pathologic status seems to us significant, and compatible with the concepts discussed later.

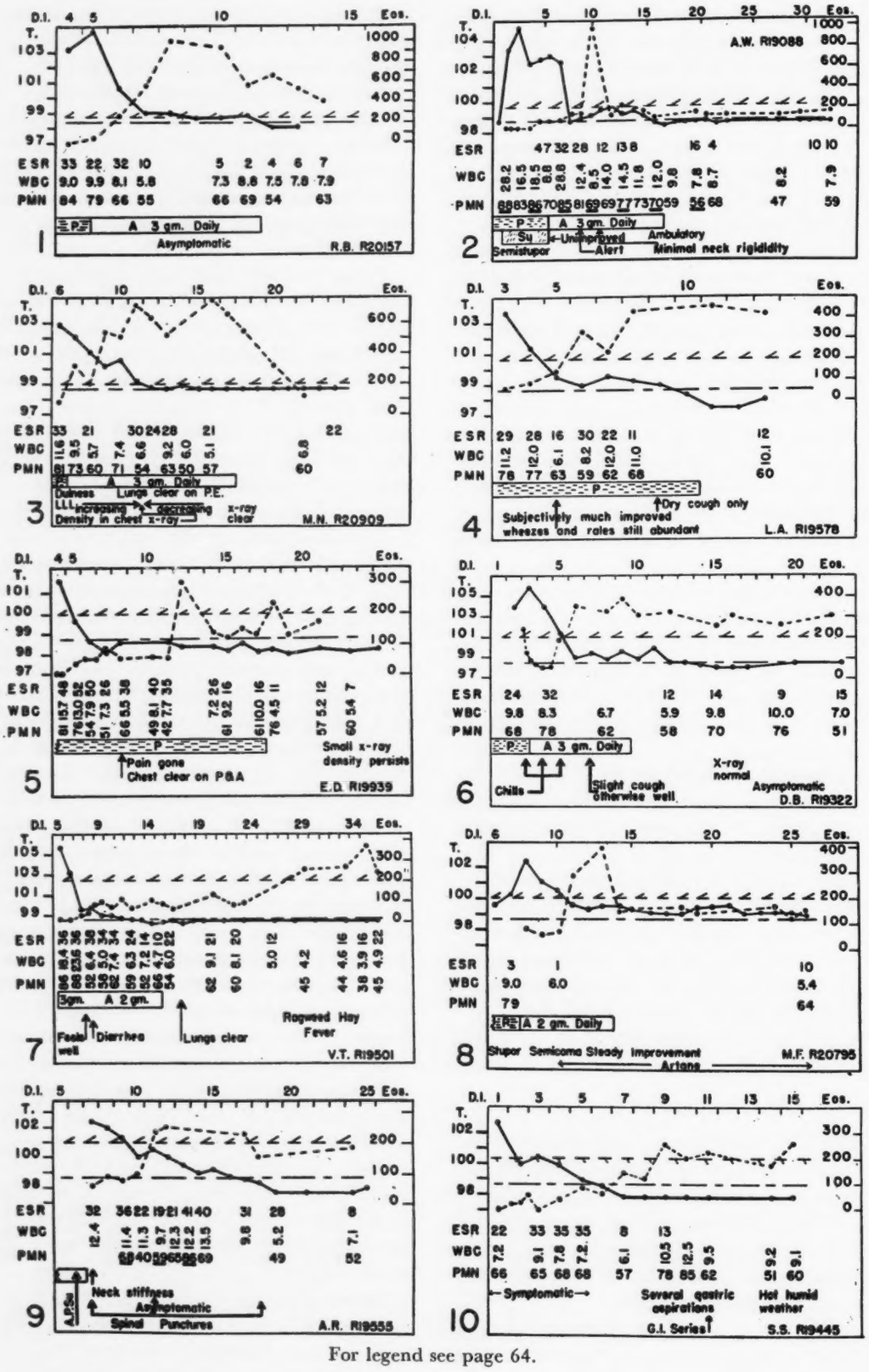
Our inability to correlate the erythrocyte sedimentation rate with the eosinopenia is not surprising since several factors are involved. Vaughan et al.[76] showed recently that the sedimentation rate cannot be used as an index of the effectiveness of ACTH or cortisone therapy even though eosinopenia is widely used.

The failure of chronic illness in our patients to influence the eosinopenic reaction is noteworthy. Unfortunately, no early counts were made in Case XXV, an apparent exception. However, marked eosinophilia is not uncommon in the later stages of malignant tumors exhibiting necrosis.[77–79]

Fever in itself has been assumed to be the common denominator in causing eosinopenia. Zappert[3] was one of the earliest to make this suggestion although even he was aware of exceptions. This thesis has recurred again and again until recently[80] but can no longer be seriously maintained as analysis of the available clinical material demonstrates. Our own data are corroborative. Altschule[81] showed clearly that the degree of elevation of the temperature had no detectable effect on the amount of change in the blood eosinophils. There is even some recent evidence[82,83] which suggests that the mechanism producing the eosinopenia depresses the fever.

Since eosinopenia occurs often simultaneously with a neutrophilic leukocytosis, the postulate of a reciprocal relationship between the neutrophil and the eosinophil, first promulgated by Ehrlich,[14] has persisted in the literature. Simon's[5] "septic factor" furthered it. Arneth[31] and Schwarz,[6] however, pointed out that the eosinopenia occurs independently of the presence of leukocytosis, and in many leukopenic diseases. Eosinopenia does not accompany physiologic leukocytosis.[7,54] The reappearance of the eosinophil in the blood, confirmed in our own cases, does not regularly parallel the fall in the neutrophil count in those patients with neutrophilic leukocytosis. It is quite probable, as recent work[84,85] has demonstrated, that such a generally reciprocal relationship exists, but it is not a necessary one. The overemphasis which it has received in the clinical literature may possibly be explained by the commonly used technic of blood counting. Reporting the varieties of white blood cells as percentage of total white cells in the blood smear tends to exaggerate inconsequential or apparent relationships.

Differences in technics of counting blood eosinophils have led to controversy. The vast majority of workers have used the ordinary stained blood smear, either slide or coverslip, and have reported the results in percentage of



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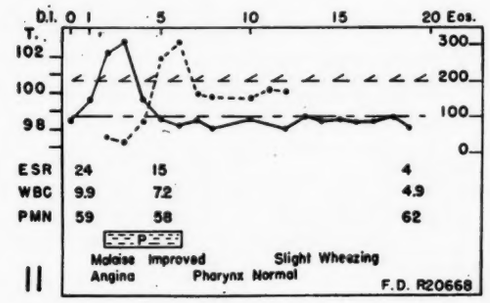

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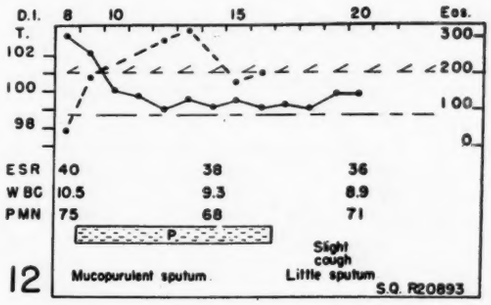

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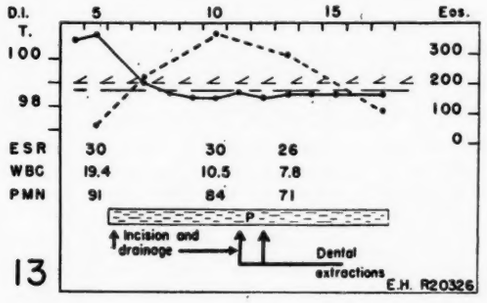

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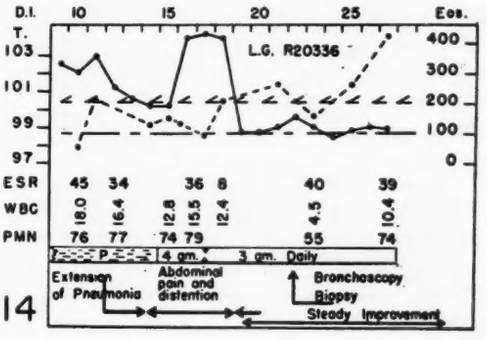
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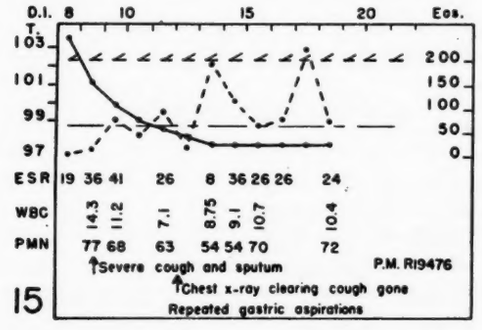
T.
L.G. R20336
ESR 45 34 36 8 40 39
WBC 18.0 16.4 12.8 15.5 12.4 4.5 10.4
PMN 76 77 74 79 55 74
P 4 gm. 3 gm. Daily
Extension of Pneumonia
Abdominal pain and distention
Bronchoscopy
Biopsy
Steady Improvement

14


D.I. 8 10 15 20 Eos.
T.
ESR 19 36 41 26 8 36 26 26 24
WBC 14.3 11.2 7.1 8.75 9.1 10.7 10.4
PMN 77 68 63 54 54 70 72
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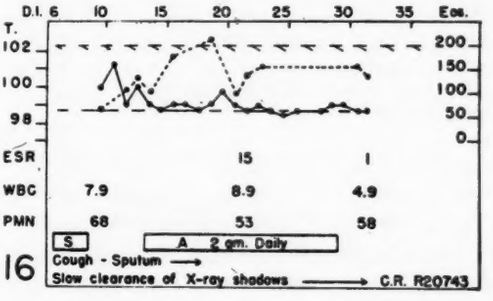
P.M. R19476
Chest x-ray clearing cough gone
Repeated gastric aspirations

15



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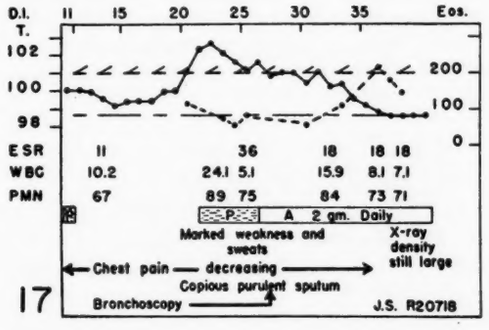

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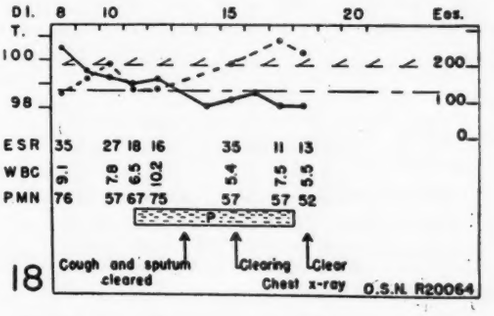
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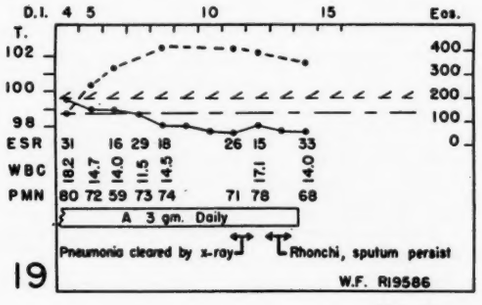
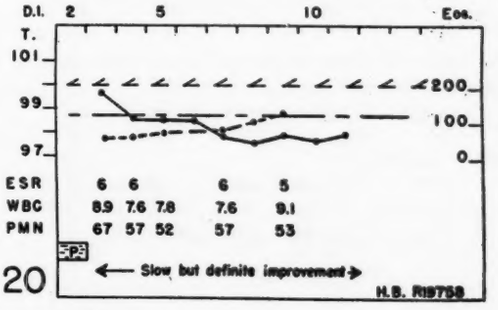
T.
ESR 35 27 18 16 35 11 13
WBC 9.1 7.8 6.5 10.2 5.4 7.5 5.5
PMN 76 57 67 75 57 57 52
P
Cough and sputum cleared
Clearing
Clear Chest x-ray
O.S.N. R20064

18


D.I. 4 5 10 15 Eos.
T.
ESR 31 16 29 18 26 15 33
WBC 18.2 14.7 14.0 11.5 14.5 17.1 14.0
PMN 80 72 59 73 74 71 78 68
A 3 gm. Daily
Pneumonia cleared by x-ray
Rhonchi, sputum persist
W.F. R19586

19



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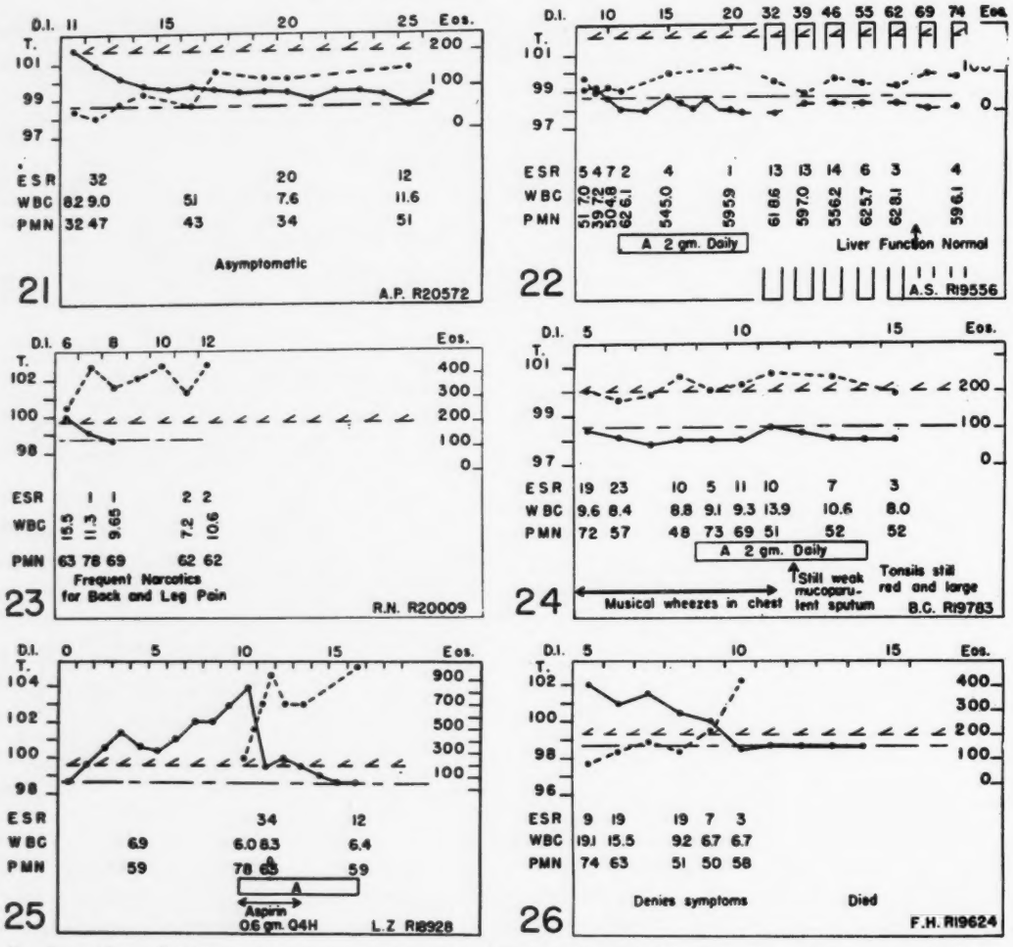

D. I. = day of illness; T. = temperature in degrees Fahrenheit —●—●—●— Eos. = eosinophils per cu. mm. – –●– – –●– – ESR = erythrocyte sedimentation rate (Wintrobe) in mm./hr.; WBC = total white blood cell count in thousands/cu. mm.; PMN = per cent of polymorphonuclear leukocytes; <<< or >>> base line (200/cu. mm.) for eosinophils; — — — base line for temperature (98.6°F.); P = penicillin; A = aureomycin; S = streptomycin; Su = sulfonamides

FIG. 1. Case I. Acute streptococcal tonsillitis.
FIG. 2. Case II. Acute meningitis, cause undetermined.
FIG. 3. Case III. Primary atypical pneumonia.
FIG. 4. Case IV. Acute pneumococcal bronchitis.
FIG. 5. Case V. Lobar pneumonia, cause undetermined.
FIG. 6. Case VI. Primary atypical pneumonia.
FIG. 7. Case VII. Pneumococcal pneumonia; ragweed hayfever.
FIG. 8. Case VIII. Pneumonia, probably atypical; Parkinson syndrome.
FIG. 9. Case IX. Probably abortive poliomyelitis.
FIG. 10. Case X. Acute pharyngitis, streptococcal and pneumococcal.
FIG. 11. Case XI. Acute streptococcal pharyngitis; bronchial asthma.
FIG. 12. Case XII. Pneumococcal bronchopneumonia.
FIG. 13. Case XIII. Suppurative cervical lymphadenitis, staphylococcal.
FIG. 14. Case XIV. Bronchopneumonia; squamous cell bronchogenic carcinoma.
FIG. 15. Case XV. Acute exudative pulmonary tuberculosis; multiple sclerosis.
FIG. 16. Case XVI. Diffuse bronchopneumonia; bronchiectasis.
FIG. 17. Case XVII. Acute lung abscess; pyopneumothorax.
FIG. 18. Case XVIII. Streptococcal bronchopneumonia.
FIG. 19. Case XIX. Bronchopneumonia; angina pectoris; polypoid sinusitis.
FIG. 20. Case XX. Streptococcal peritonsillar cellulitis.
FIG. 21. Case XXI. Infectious mononucleosis.
FIG. 22. Case XXII. Infectious hepatitis.
FIG. 23. Case XXIII. Upper respiratory infection; herniated nucleus pulposus of lumbar spine.
FIG. 24. Case XXIV. Tonsillitis, probably streptococcal; asthmatic bronchitis.
FIG. 25. Case XXV. Bronchogenic carcinoma; ? pneumonia; pulmonary cystic disease.
FIG. 26. Case XXVI. Acute myocardial infarction.

white cells. The direct count in the chamber and the reporting of eosinophils in absolute numbers has been used only sporadically until recently. It was recommended, however, as long ago as 1888 by Mayet[86] and subsequently emphasized and refined, especially by Zappert,[3,17] Dunger,[26] v. Domarus,[49] Rud[7] and Randolph.[68,69] Of the two methods the former has been criticized as inaccurate and misleading; the latter is now considered to be the method of choice.[3,7,17,49,75]

It was emphasized earlier in this report that the eosinopenic response was not a function of the specific disease entity, as was implied by many authors, but a non-specific reaction. From our observations and from published material the conclusion seems inescapable that the fall of circulating blood eosinophils is best correlated with the acuteness and the severity of the clinical condition. These terms are not easily definable but the general validity of the relationship is difficult to dispute. The mechanisms operating appear to be identical with those of Selye's[84,85] "alarm reaction."

The now well known "alarm reaction" was first described[87] in 1936. That a fall in circulating blood eosinophils is a constant feature of the "alarm reaction" was further postulated in 1939 by Dalton and Selye.[88] In the course of his development of the concepts of the "alarm reaction" and "general adaptation syndrome" Selye[84,85] surveyed exhaustively a tangled mass of heterogeneous phenomena which he unified into acute and chronic stress phenomena.

These phenomena were foreshadowed, often to a surprising degree, by the literature on the eosinophil. In 1893 Zappert[3] showed that the circulating blood eosinophils fell after tuberculin injections. Capps[89] in 1896 observed that several hours after severe convulsions in paretics the eosinophils decreased. In 1910 Stäubli[90] described eosinopenia following experimental intravenous or intraperitoneal administration of egg albumin, bouillon, water and even physiologic saline. In 1931 v. Domarus[49] summarized his conclusions of many years' work, "Bei konsequenter Anwendung der Kammerzählung der Eosinophilen liess sich bei einer grossen Zahl von Patienten der verschiedensten Art in zahlreichen Fällen ein von der Norm abweichendes Verhalten in der Sinne konstatieren, dass auf der Höhe der Krankheit eine mehr oder weniger starke Verminderung oder vorübergenhend sogar völliges Schwinden dieser Zellart beobachtet wurde. Dieses bisher in der Hauptsache nur von den Infektionskrankheiten her bekannte Phänomen kommt, wie unsere Beobachtungen lehren, tatsächlich in gleicher Weise auch bei zahlreichen anderen nichtinfektiösen Krankheiten vor. Neu ist hierbei u. a. die Erkenntnis, dass die Verminderung der Eos. zum Teil auch bei klinisch leichten Erkrankungen vorkommt. *Die Eos. erweisen sich hier als ein sehr feiner Indicator einer vorübergehenden und flüchtigen Schädigung des Organismus.*" (Italics ours.)

Similar findings were reported by others. Brown[4] in 1903 stressed the favorable prognostic significance of the presence of the eosinophil in various surgical conditions. Krumbhaar[91] in 1917 commented on the decrease or disappearance of eosinophils for many hours postoperatively. These findings have, of course, been amply confirmed and extended recently.[92–97]

When Bertelli, Falta and Schweeger[98] in 1910 published their comprehensive experiments in dogs and in man, the fact was already well known that epinephrine, given parenterally, will cause a sharp drop in circulating eosinophils within four to five hours. This was confirmed by others and especially by Rosegger[99] in 1933 but seemed to be of little practical importance until recently.

In 1948 Hills et al.[100] showed that ACTH produced eosinopenia by stimulating adrenocortical secretion. Shortly after this discovery Forsham[100] and Thorn[101] proposed the use of ACTH as a test of adrenocortical function. Following Godlowski's[103] and Laragh and Almy's[104] revival of interest in the eosinopenic potentialities of epinephrine, and Recant et al.'s[105] demonstration that the effectiveness of epinephrine was due to stimulation of the pituitary-adrenocortical system, this drug was adopted for practical use as a test of the integrity of the system.

It is now clear that in acute infectious disease the body reacts, as it does to other forms of stress, by stimulation of the pituitary-adrenal system. Among the resulting phenomena is a reduction in eosinophils, the degree of reduction varying directly with the severity of the stress. As Selye[85] has emphasized, the phenomena produced by any insult to the organism is compounded of both specific and non-specific factors. In any specific disease or infection these cannot always be disentangled and it is often difficult to correlate consistently many signs and symptoms, e.g., leukocytosis, fever. It is all the

more remarkable that eosinopenia is one of the more constant of the non-specific reactions whether it occurs in the course of disease or in the course of stimulation by epinephrine, cortisone or ACTH, and suggests that the eosinopenic response is probably a primitive one.

These recent investigations have again stirred up interest in many dormant but unanswered questions about the eosinophil cell. It is now reasonably clear that protein or a derived molecule and the immune process are involved in the cell's activities. However, attempts to relate it to antibody[106] or antigen-antibody reaction[11] have not been conclusive. The function of the cell is an almost complete mystery.

Equally mysterious is the fate of the eosinophils. The cells disappear from the blood rapidly. Where do they go, and what happens to such hardy cells? In high grade eosinophilias, such as found in Loeffler's syndrome or tropical eosinophilia,[107] parasitic infestation[108] and even eosinophilic leukemia,[109] fantastic numbers may disappear following epinephrine or ACTH injection. There is some evidence to indicate that the disappearance of the cells from the blood is not due to failure of production by the bone marrow[103,110] nor to their destruction in the spleen,[97] although temporary storage in the spleen has recently been suggested.[111] Josey[50] in his studies on experimental peritonitis found an increase in eosinophils in the peritoneal fluid simultaneously with a fall in the blood and suggested this as at least one possible mechanism. McNeil[112] injected rabbits cutaneously with Eberthella typhosa and studied lymph nodes by differential counts before, and for fifteen days after, injection. Within a number of hours the lymph nodes showed eosinophilic cell infiltration which lasted for forty-eight hours. The eosinophils seemed to disintegrate eventually in the lymph nodes. Last's[113] recent studies on dogs suggest that the eosinophil may disappear from the blood very rapidly, without apparently being destroyed. Following histamine injections he noted two types of eosinopenic response, an immediate precipitous drop within ten to fifteen minutes and then a slow rise within the next two to three hours to the levels of the delayed ACTH or cortisone type of response with a subsequent slower eosinopenic slope.

What is the mechanism of postinfectious eosinophilia? The different morphologic and biochemical phenomena which are precipitated during stress (natural or ACTH and cortisone-induced) disappear during the "stage of resistance" and in many instances the direction of the change is reversed.[84] For instance, hypochloremia during the "alarm reaction" is followed with hyperchloremia during the "stage of resistance." The 17-ketosteroids show increased urinary excretion for one to three days following stress but then decrease to below normal until returning to normal late in convalescence.[114] This strong reversal of direction seems more than simple rebound and is analogous to the behavior of the eosinophils in infectious disease. Mild postinfectious eosinophilia possibly is understandable as simple physiologic overshooting. However, the frequent height and duration of the eosinophilic rise, with even intense eosinophilia, indicate that this is at best a very limited explanation. The eosinophilias of infectious disease are probably the resultant of nonspecific and specific factors (protein factors in the immune process), with the latter playing the stronger role.

One of the more intriguing problems, posed recently, is the function in body homeostasis of the increase in adrenocortical function during acute infections. It has been assumed, reasonably, that this is chiefly a protective factor. In adrenalectomized animals, as well as in patients with Addison's disease, the lack of resistance to infections and other forms of stress is overwhelmingly documented.[115,116] From these facts has evolved the clinical concept of adrenal exhaustion which occurs, under continuous severe stress, in animals and patients with intact adrenals. In grave infectious disease adrenal damage is frequently invoked as a deleterious factor and has been assigned a major role in the so-called Waterhouse-Friderichsen syndrome.[117] However, numerous attempts, by means of treatment with ACTH or adrenal cortical hormones, to increase the body's resistance under such circumstances have essentially failed.[84,118] Furthermore, as pointed out earlier in this paper, the more severe the infection the more depressed is the eosinophil count. In fulminating and fatal infections the count falls to zero early in the course and remains there until the patient's death. This was one of the facts on which the prognostic value of the eosinophil count was based. Since the eosinophil is an exquisitely sensitive indicator of adrenocortical activity, the more logical deduction would be to postulate increased rather than

decreased activity. By such a criterion the administration of cortical hormones during severe infections and stress would appear to be illogical and possibly harmful. Recent data bearing on such a possibility are of interest.

Thorn et al.[119] noted the failure of ACTH to prevent the development of herpes zoster in one patient, varicella in another and herpes simplex in several others. Similarly, cortisone did not prevent the development of herpes zoster in two patients.

Tuberculosis is now considered to be a definite contraindication to the use of either ACTH or cortisone. Clinical and experimental studies[120–125] have amply confirmed the rapid amelioration of clinical signs and symptoms accompanied, however, with enhanced growth of the tubercle bacilli in the lesions and further spread of the disease.

Kuzell and Mankle[126] produced polyarthritis in rats with an L4 strain of a pleuropneumonia-like organism. Cortisone and terramycin were compared in their effectiveness as preventive and therapeutic agents. Terramycin was effective but rats receiving cortisone "looked worse at the end of the experiments and weighed less than the controls."

Turner and Hollander[127] found large numbers of Treponema pallida in experimental syphilomas in rabbits treated with ACTH and cortisone. When the cortisone was withdrawn, a rebound phenomenon occurred in which the syphilomas reached unusual size.

Kass et al.[128] treated three patients with pneumococcal and two with atypical pneumonia with ACTH. Defervescence and clearing of toxic symptoms were prompt. Despite this the bacteremia persisted in one patient and the rusty sputum in another. The pneumococci in the sputum were not phagocytosed by the polymorphonuclear leukocytes. One patient with pneumococcal pneumonia had an exacerbation of symptoms while under ACTH therapy, and he later developed empyema.

Glaser et al.[129] found that mice experimentally infected with group A streptococci did less well when treated with ACTH or cortisone than when untreated.

Mogabgab and Thomas[130] infected rabbits intradermally with hemolytic streptococci. Using the same dose in all animals, no death occurred in the controls. In animals pretreated for four days with 50 mg. cortisone daily, septicemia and death occurred in all, two to twelve days after infection. Histologic study showed, in the latter group only, dense deposits of cocci, myocarditis and glomerulonephritic-like lesions.

Shwartzman[131] concluded in recent studies that the susceptibility of mice and hamsters to experimental poliomyelitis is enhanced by cortisone.

Following Smadel et al.'s[132] demonstration that patients with typhoid fever showed rapid clinical improvement under combined cortisone and chloramphenicol treatment, Woodward et al.[133] treated seven patients with typhoid fever with cortisone alone. The clinical manifestations of the disease were controlled quickly. However, bacteremia and positive stool cultures persisted in several patients and two eventually received chloramphenicol. In one of the latter patients pericarditis was first noted several days after completion of the cortisone therapy.

In growing the viruses of influenza (PR 8 strain of A and Lee strain of B) and mumps (Habel strain) in chicken embryos, Kilbourne and Horsfall[134] found the viral concentration in the allantoic fluids of cortisone-infected eggs to be over 100 to 600 per cent greater than in the control eggs.

Using the PR 8 strain of influenza A, Loosli et al.[135] studied the course of experimental airborne infection in mice. ACTH appeared to have a deleterious effect as indicated by the higher mortality rates in infected mice treated with this hormone.

There seems little doubt from the foregoing data that ACTH and some adrenocortical hormones may have an adverse effect on acute infections *in vivo*. The total disappearance of circulating blood eosinophils in very severe infections suggests that a high degree of adrenocortical activity is important. Quantitative data on experimental animals are fragmentary but there is some evidence that the size of the hormonal dose plays a significant part.[135,136] How general these effects are, or what role the animal species, the type of hormone, the antigen-antibody mechanism and a host of other factors play, is not evident at present. A few of these factors are reviewed in a recent article by Kass and Finland.[137] We believe the following to be a reasonable working hypothesis in clinical acute infectious disease: any infection sets off the protective "alarm reaction," which in mild or moderate infections is replaced fairly soon by the body's usual defenses against infection. In fulminating infections the "alarm

reaction" is more violent; there is intense adrenocortical secretion, followed with further spread of an already virulent process, followed in "vicious cycle" fashion by further intensification of the adrenocortical activity.

SUMMARY

Recent revival of interest in the eosinophil cell is a by-product of the current intensive research into the function of the adrenal cortex.

A historical survey of the eosinophil reveals an enormous mass of frequently controversial data which has accumulated during the past seventy years. These data have produced very limited conclusions about the cell proper, eosinopenia and eosinophilia. The function of the eosinophil is still largely a mystery.

In acute infectious disease the prognostic significance of the circulating blood eosinophils has been known for many years. Their decrease or absence was considered a serious omen, their presence or reappearance a good clinical sign.

For several reasons the role of the eosinophils in acute infectious disease is worthy of restudy: (1) Emphasis, until very recently, has been on their behavior as a manifestation of a specific disease. Their essential non-specificity went either unnoticed or was underemphasized. (2) That eosinopenia is of significance, or that it occurs at all, has been widely ignored in this country. (3) Correlation of the older data with the newer concepts may be productive.

Twenty-six unselected patients taken from the routine admissions to the Infectious Disease Ward were studied. Serial blood eosinophil counts were made by means of the Randolph chamber technic and the results were correlated with a variety of items. The best positive correlation was achieved with the clinical appearance of the patient.

Decrease or disappearance of the circulating blood eosinophils has been shown to be a sensitive as well as a constant indicator of increased adrenocortical function. This occurs in man and animals in various forms of stress, as the "alarm reaction" of Selye or after the administration of ACTH or cortisone. The eosinopenia of acute infectious disease is a manifestation of the "alarm reaction."

The fate of the eosinophil which disappears from the blood is unknown but the cell is probably not destroyed immediately.

So-called postinfectious eosinophilia is probably a combination of many specific and non-specific factors.

Recent evidence has been accumulating to indicate that adrenocortical hormones may have a deleterious effect on certain acute infections in man or animals with intact adrenals. This mechanism may be operative in fulminating infections.

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Seminars on Gastrointestinal Physiology

A Physiologic and Clinical Consideration of the Pressures Developed in the Digestive Tract*

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PAST experiences have demonstrated the advisability of critically evaluating at intervals the technics employed in studying a phase of basic and applied physiology. Such an evaluation tends (1) to emphasize the desirable aspects of the available methods and also their inadequacies and (2) to indicate the general type of new methods which should be developed. Since our knowledge of any research field is highly dependent on the intelligent application of adequate investigational methods, a serious consideration of "methods" is warranted.

These ideas apply especially to studies of the pressures developed in the digestive tract for (1) the inaccuracies and limitations of older research methods in this field were not accurately appreciated; (2) several investigational methods recently made available need comparison with older methods which they supplant or complement; (3) considerable re-emphasis has developed on gastrointestinal studies to correct or advance basic knowledge regarding this system in health and disease, and also for evaluating the actions of new drugs, the effects of ionizing radiation, the effects of emotional states, etc.

Some research methods can be recommended because they are relatively simple. The technic may be easy to learn or relatively simple apparatus may suffice. However, exact information usually is obtained only by employing considerable technical skill or the use of complex equipment. No royal road leads to the secrets of gastrointestinal function. A false sense of accomplishment may be associated with certain simple technics and the incautious worker may easily collect many records but obtain little significant information.

The major activities of the digestive tract involve (1) the formation of secretions, (2) the absorption of gut contents and (3) the development of pressure. Pressure development is most strikingly illustrated in the oral cavity where skeletal muscle contractions may produce pressures of 200 pounds per square inch between opposing molar teeth. Adequate mastication makes the food more plastic, less traumatizing and greatly facilitates the subsequent propulsion of food along the gut. By increasing the surface area of the food particles, mastication augments the contact between enzyme and substrate and thus facilitates digestion. Pressures developed by contractions of the gut wall are responsible for the additional crushing and mixing of food which occurs in the remainder of the digestive tract.

Propulsion of material along the digestive tract is dependent on a pressure gradient between two adjacent sections.[1,2] The expulsion of the gut contents by vomiting or defecation depends on the presence of the material at the appropriate body orifices at pressures exceeding atmospheric pressure. Such expulsion of the contents may result from pressures produced entirely by gut contractions as occurs in regurgitation of gastric contents or the involuntary passage of flatus or feces. Usually the pressure gradients involved in vomiting or defecation result from a combined contraction of the gut

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muscle and the simultaneous contraction of the diaphragm and abdominal muscles. The resulting general increase of intra-abdominal pressure is transmitted to the contents of the digestive tract and promotes their evacuation. The general increase in intra-abdominal pressure developed by straining, coughing or retching produces a pressure gradient between the gut contents and the outside; but since it does not produce a localized pressure differential between adjacent parts of the tract, it usually does not cause propulsion or the expulsion of the gut contents especially when the sphincters are competent.

Moderately increased intralumen pressure within the gut is one of the most common and effective stimuli for augmenting gastrointestinal motility. The increased intralumen pressure and the associated stretching of the stomach or the intestine by the entrance of a meal effectively augments gastric[3] or intestinal secretion[4] and may also modify intestinal absorption.[5]

Excessive pressures develop in the gut lumen when the following conditions act independently, or more frequently, simultaneously; (1) excessive quantities of material are introduced into the gut through one of its orifices or is secreted by its glands, (2) faulty propulsive activity fails to distribute or expel the contents and (3) an obstruction of the tract prevents adequate propulsion.

Excessive intralumen pressures result from overeating or drinking, excessive air swallowing, acute gastric dilatation, postoperative distention, intestinal obstruction, imperforate anus, etc. The exaggerated effective intralumen pressures developed during marked and sudden reductions in ambient pressure associated with the ascent of aviators or deep-sea divers has received much attention.

Excessive intralumen pressures in the digestive tract may produce pain, collapse, respiratory and cardiovascular irregularities, vomiting, a general inhibition of gastrointestinal motility, accumulation of digestive secretions, interference with the blood flow (especially the venous return) in the distended region, gangrene and perforation.[6–8] The development of a pressure gradient between the gut lumen and the abdominal cavity is essential for the final perforation of a penetrating ulcer of the alimentary tract and for the escape of contents through the opening. By accurately recording pressures from the gut lumen and immediately adjacent to it in the abdominal cavity we have observed large pressure gradients between these areas associated with vigorous peristaltic contractions.[9] Such gradients could perforate weakened portions of the gut wall or discharge gut contents into the abdomen through a suitable perforation.

Accurate registration of intralumen pressure from the gut is predicated on an appreciation of the physical factors involved in the production of these pressures. An increase of intralumen pressure in a segment results from a force (usually produced by contraction of the muscular coats) which tends to reduce the volume of the segment. The pressure is related to the magnitude and rate of the volume change. Such a reduction of volume expels some of the segment contents but this tendency is opposed by a resistance from adjacent structures to this expulsion. The pressure, $P = (dV/dt)\ R$, where dV/dt represents the time rate of volume change and R represents the resistance to escape of the segment contents; $1/R = 1/R_o + 1/R_a$, where R_o is the resistance to the orad escape of segment contents and R_a the resistance to analward expulsion.

The character of the problem of intralumen pressure registration was not carefully analyzed and the essential technic was not applied to digestive tract studies prior to 1938. The term "pressure" was uncritically applied to records from apparatus which incorporated one or more vitiating factors and thus was incapable of accurately recording gut pressures. Frequently, a thin-walled naked balloon of condom rubber was placed in the gut lumen via the oral or anal opening or by fistulas and connected to a sensing-device. Small balloons were employed to record from a small area. If the balloon was large, it constituted a foreign body which might seriously modify motility in the gut segment. The pressures developed within a balloon represented the algebraic sum of the numerous pressures acting on the balloon periphery. Thus a contraction on one portion of a large balloon might be counterbalanced by relaxation in an adjacent region; the record would indicate pressures different from those developed by the segment containing no balloon. Multiple or tandem balloons recording from contiguous areas provides more satisfactory information regarding motor activity from an extensive portion of the gut.

A contraction wave in a gut segment produces pressures within the balloon lying in the segment

which vary according to the size and shape of the balloon. Thus the intraballoon pressure may vary greatly from the intralumen pressure. Also the balloon constitutes an artificial cavity which offers an artificial resistance to the orad and aborad escape of contents, i.e., its R_o and R_a may be related more to the balloon elasticity than to the R_o and R_a naturally occurring in the segment. For example, if the gut at either end of the balloon were patulous, the segment R_o and R_a would be essentially zero and a contraction at the balloon site would develop practically no intraluminal pressure. However, such a contraction should develop significant intraballoon pressure since the balloon wall provides values for R_o and R_a which are related to the balloon elasticity.

The pressure-sensing device requires some volume change to "drive" it. This volume change is significant when water or bromoform manometers or loose tambours are employed. Thus a *complex* of the pressure and volume change within the gut segment is recorded which has defied accurate interpretation. This error is diminished by employing devices with lower volume/pressure ratios such as the mercury manometer or spoon capsule. The inertia of all these devices except the spoon capsule is much too great for accurate registration of the rapid components of the pressure changes we have recorded from the gut with adequate equipment.[9,10] We have given this subject rigorous theoretic and experimental consideration in previous publications.[2,10]

If a water or bromoform manometer or loose tambour having a high volume/pressure ratio is employed, sufficient escape of segment contents occurs through the artificial channel to lower the intralumen pressure significantly. Thus in the formula $P = (dV/dT) R$, a factor R_m (resistance of flow into the manometer) is added and $1/R = 1/R_o + 1/R_a + 1/R_m$. With pressure-sensing devices having a high volume/pressure ratio, R_m is small and may greatly modify the intralumen pressure. Such apparatus may be incapable of recording the maximal intraluminal pressures which are developed for the total contents of the segment may be inadequate to drive the sensing-device to the true pressure. We emphasized this failure by recording with adequate equipment pressures exceeding 100 cm. in a gut segment having an estimated volume less than 5 cc. If the same segment were connected to a common water manometer having a volume/pressure coefficient of 0.5 cc/cm., the maximal pressure to which the manometer could be driven by expelling all the segment contents through the artificial channel would be less than 10 cm.

If a definite volume of air is introduced into the balloon-manometer system, first with the balloon in air and later with the balloon in the gut, the differences in pressure developed within the system roughly measures the gut tone ("resistance of the muscle to a stretching force") at the location of the balloon. Similarly, a crude determination of muscle tone ("resting length of the muscle") can be obtained by comparing the volume of air which must be introduced into the system to produce a certain pressure, first when the balloon is outside the body and second after the balloon is in the gut. Many investigators employ these technics without appreciating what can be accomplished by them or especially the limitations of the methods. The method favored by an investigator or the modifications of technic introduced by him has usually been determined by individual prejudice rather than an appreciation of the problems in physics involved or the suitability of the apparatus to the investigation.

If the quantity of air introduced into the balloon is sufficient to stretch the gut, contractions are initiated and the record represents the "induced" activity rather than the "spontaneous" activity. The balloon which is inflated enough (probably above 10 cm. water pressure) to interfere with venous return in the stretched area simulates digestive tract obstruction and thus is abnormal. Such excessive stretching may greatly modify or even reverse the effects of stimuli.[11,12]

Significant reproductions of the normal motor activity in that portion of the tract in which the balloon lies can only be obtained provided the subject is unanesthetized and free of physical or mental traumatic factors. This necessitates *extensive training* of the animal or human subject. Investigators who ignored this requirement and studied untrained subjects obtained records greatly influenced by vitiating factors. Such records have served chiefly to re-emphasize the high susceptibility of the gut to disturbing mental upsets or physical distress and have confused more then they have contributed toward a solution of the primary problems of the investigation. Hard, rigid or rough tubes have been employed to connect balloons to the sensing-device. The distress produced by such tubes

certainly militates against the production of normal motor activity by the gut.

The balloon-water manometer technic will continue to find extensive use in studies on the digestive tract. It provides a relatively simple method of recording what may be expressed by the inexact term "motor activity" of the gut. The device cannot measure any activity precisely and it is erroneous to express the results of such studies in terms which imply anything more than rough approximations. Accordingly, the results obtained from simple forms of the balloon-water manometer can be about as satisfactory as from more elaborate forms of this device. "Improvements" on the construction of this device or the interpretation of the records it produces usually do not contribute a real advance; they may actually be objectionable by producing a false promise of progress or by obscuring the fundamental factors.

Most of the inaccuracies in pressure registration which are inherent in balloons may be avoided by recording from open-ended tubes placed in the gut lumen. If they are combined with a pressure-sensing device of low volume/pressure ratio, accurate pressure registration can be achieved. A satisfactory pressure pick-up *combined* with a satisfactory pressure-sensing device is essential to accurate pressure recording. Improving only one component accomplishes little more than a false sense of achievement as is illustrated by the balloon-spoon capsule combination. If the open tube within the gut is attached to a water manometer (Schreiber[13]), a significant artificial channel is provided for the escape of gut contents and the intraluminal pressure is reduced. Also if much of the gut contents enters the tube, it damps or blocks the pressure variations transmitted to the recorder. When the pressure-sensing device has a low volume/pressure coefficient, sufficient gut contents do not enter the open tube leading from the gut lumen to prevent accurate pressure registration. However, when air conduction is employed, high intralumen pressures will compress the air and will force significant volumes of contents into the tubing. By catching this in expanded tips, obstruction of the connecting tubing is avoided. We have also found it advantageous to maintain a flow of 2–4 cc./hour of the pressure conducting gas or liquid into the system from an appropriate "bleeder." This subterfuge keeps the open tip cleared but does not interfere with accurate pressure registration.

We originally recorded intralumen pressures acurately by air transmission through a small bore open-ended tube to an optical manometer of small internal volume.[1,14] Air transmission permitted us to set our apparatus at atmospheric pressure without the corrections for hydrostatic pressure which are essential with liquid transmission. The open tube-optical manometer technic seems to us especially satisfactory for investigating human subjects. We have also developed or adapted several electrical substitutes for the optical manometer. Although they require somewhat more expensive equipment, they are well suited to studies on dogs or humans especially since they permit alteration of the sensitivity of the recorder over a wide range during the experiment.

Since the movements of the gut are relatively slow, it might be assumed that the associated changes in intralumen pressure are equally sluggish and that the faithful registration of such changes would not exceed the dynamic capabilities of so sluggish a device as a water manometer. However, with adequate apparatus having little inertia, we demonstrated the occurrence of unexpectedly rapid changes in intralumen pressures. In some instances the pressure rose in an essentially linear manner from basal to maximal value within one second. Decay to basal pressure occurred during the succeeding second. An analysis of manometer dynamics has shown that the conventional water manometer has a natural frequency less than 1 cycle/second and is incapable of faithfully following such rapid pressure changes.[10] A manometer possessing a natural frequency of 30 cycles/second will provide an excellent reproduction of the pressure waves occurring in the gut; usually a frequency of 15 per second is satisfactory. Since the natural frequency of a manometer is directly proportional to its "rigidity," the smaller its volume/pressure coefficient the higher will be its natural frequency. If a pressure-sensing device is "rigid" enough to satisfy the volume change requirements of intralumen manometry, it usually will also be "rigid" enough to satisfy the dynamic response requirements.

The two-channel optical manometer apparatus which we employed extensively in the registration of intralumen pressures from the human gastrointestinal tract is shown in Figure 1. Intralumen pressures exerted against the mouths of two open-ended soft plastic tips (length 1.1 cm., external diameter 5.1 mm., internal

bore 3.8 mm.) are transmitted by air along narrow bore plastic tubing (internal diameter 0.75 mm.) to optical manometers of 0.06 cc. internal volume. The manometers are capped with thin rubber membranes stretched to about four times their unstretched dimensions. A vulcanite peg, 1 mm. in diameter and 1 mm. tall, is cemented eccentrically on each membrane. A mirror consisting of a small square of 0.5 diopter plano-convex lens silvered on the plane surface, is mounted on each peg. Bulging of the membrane induced by the transmitted intralumen pressure causes rotation of the mirror about the base of the peg and corresponding deflection of the reflected beam on the photokymograph.

A third tube, which terminates in a distally located balloon, is bonded with the two open-ended tips into an integral unit. During use the remainder of the tubing lengths are loosely held together by a sheath of ¼ inch Penrose rubber drainage tubing. A small amount of mercury in the balloon assists in passing the tubing assembly through the pylorus if areas beyond the sphincter are to be investigated. After the desired positioning of the open tips has been accomplished under fluoroscopic guidance, the mercury is usually aspirated from the balloon and thus further wandering of the open tips is minimized.

The oro- and nasopharynx of the subject are anesthetized by the topical application of 2 per cent butycaine sulfate. The subject then swallows the tubing assembly. When the distal end of the assembly has reached the vicinity to be studied, the proximal ends are connected to an intranasal catheter which is then retracted so the final route of the tubing assembly is pernasal. During the introduction and localization of the manometer tubing, plugging of the tubing with gut contents is prevented by moderately taut condom rubber membranes tied over the open ends of the tips against thin brass ring inserts. After localization of the tips has been achieved, the protective membranes are ruptured cleanly by rapidly injecting 5 cc. of air into the tubing.

The natural frequency of each manometer and its associated components under conditions of use is approximately 25 cycles/second. The dynamic damping ranges from 50 to 100 per cent of the critical value depending upon the viscosity of the gastrointestinal contents. The total volume of each manometric system is 0.8 cc. and the volume of each open tip is 0.1 cc. These manometers are capable of recording a rise of intralumen pressure of 150 cm. of water before the resulting compression of the transmitting air column causes the passage of intestinal contents beyond the open tips into the narrow bore connecting tubing. The 0.1 cc. volume change associated in this apparatus with a rise in intralumen pressure to 150 cm. of water is contrasted with the 75 cc. volume change which would be necessary to "drive" the average water manometer to this pressure. Our recent refinements[9] in the open tube technic produced apparatus which requires less than 0.02 cc. volume change to "drive" it to a reading of 150 cm. of water pressure. This apparatus can record pressure to a maximum of ±1,000 cm. of water.

An electrical pressure transducer having the dead space filled with a liquid is much more "rigid" than an optical manometer. The resultant decrease of compressible volume permits a satisfactory dynamic response when such a transducer is recording from the gut lumen through significantly smaller tips and connecting tubing than was required by the optical manometer. In animal experimentation open-end tips 8 mm. long and 3 mm. wide are satisfactory. The tubing which connects the open-end tip to the transducer has an external diameter of 0.75 mm. and a bore of 0.4 mm. The internal compressible volume of this device is only 0.1 cc. and it is capable of recording more than 650 cm. of water pressure before gut contents enter the connecting tube. This capacity for recording high pressures has proved valuable since we have frequently recorded phasic pressure spikes of approximately 475 cm. of water from the canine gastrointestinal tract. When the length of the connecting tubing is increased sufficiently to be applicable in human studies, the dynamic response of the apparatus becomes seriously overdamped. This defect is readily corrected by substituting hydrogen for air as the gaseous pressure-conducting medium in the connecting tubing.

A number of electrical pressure transducers are now commercially available. We employed[10] two of the "variable capacitor" type (Sanborn Electromanometer and Technitrol's Lilly manometer) and one of the "unbonded strain gauge" type (Statham Laboratories). The variable capacitor types proved unsatisfactory due to excessive instability in the high sensitivity ranges. The Statham transducer (Model P23-15G-2000), when employed with a carrier-type

bridge amplifier of our design, is adequately stable at any desired sensitivity range. The commendable aspects of this strain gauge arrangement are emphasized by the observation that it is capable of essentially the same sensitivity as the water manometer (0.5 cm deflection per cm. water pressure), its dynamic response is approximately 40 times that of the water manometer and it requires only about $\frac{1}{5000}$ as much volume change to "drive" it.

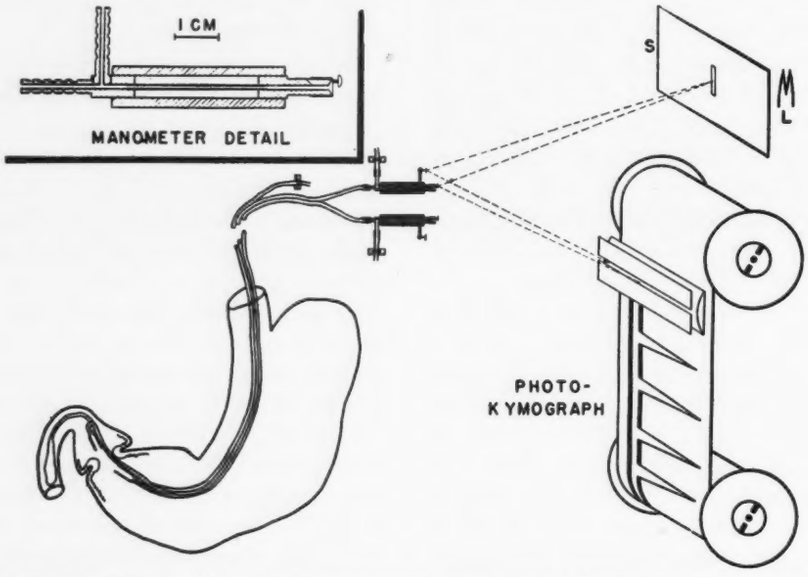

FIG. 1. Apparatus for accurate, continuous registration of intralumen pressures from the upper digestive tract.

Because the internal volumes of our manometric systems are so small, even minute leaks will eventually permit gastrointestinal contents to enter the connecting tube. In earlier apparatus, such as shown in Figure 1, plugging of the connecting tube was prevented by forcibly injecting a small quantity of air into a side tube at ten- to fifteen-minute intervals. The "bleeder" technic has now supplanted this procedure. Air under approximately half an atmosphere of pressure is permitted to leak into the side tube through a very fine constriction at the rate of 3 to 5 cc. per hour. This rate of flow keeps the tubing free of obstructing material without affecting the desirable characteristics of the system. The "bleeder" technic also insures a sufficient volume within the tubing to "drive" the manometer.

We have substituted normal saline solution for the gaseous pressure-transmitting medium and thus have eliminated the enlarged open-end tip. In this technic saline bleeds into the system instead of air. This modification, applied to the strain gauge transducer described above, resulted in a technic suitable for use in animals in which the only foreign object in the gut lumen is a short length of soft plastic tubing 1.25 mm. in external diameter. This is the most physiologic pick-up device we have achieved. The open tip records essentially from a point in the gut lumen. We observed that the gut tends to form isolated cavities or pockets, and the open-tip would accurately record the pressure existing in one of these pockets. The balloon would record the motor activity existing within an area of a size partly determined by the size of the balloon.

The methods we developed for the accurate registration of the pressures within the gut are applicable to the registration of the pressures developed in other cavities. As an example of such an application we punch a number of small perforations into the distal $\frac{1}{2}$ cm. of such tubing as is described above, introduce it directly into the peritoneal or thoracic cavity through a No. 15 needle, and employ it for accurately recording intraperitoneal and intrathoracic pressures by a technic similar to that employed for digestive tract studies. This is the first application of a method which meets the physical requirements for the accurate registration of intraperitoneal and intrathoracic pressures.

The technics for accurate intralumen pressure registration we have described thus far have all been of the pressure conduction type. That is, pressures developed within the gut lumen are

transmitted to an external pressure-sensing device. Such technics are both physically and physiologically adequate, but they impose considerable restriction on the movement and position of the subject. Furthermore, since the total internal volume of the device should be low, the connecting tube should be relatively short. To overcome this difficulty we constructed pressure transducers small enough to be introduced directly into the lumen of the gut so the connection between the internal and external members of the apparatus was electrical rather than hydraulic. Subminiature transducers based on the principle of the carbon button microphone, the variable electrolytic cell and the variable capacitor gave us only partial satisfaction. We recorded[10] intralumen pressure with some success using our modification of the miniature differential transformer originally designed by Wetterer.[15] Hightower[16] also reported encouraging results when recording intralumen pressure with the Gauer modification of the differential transformer principle. However, this claim becomes suspect since the *in vivo* transducer appeared to give the same pressure values as a balloon in the same portion of the gut. At present some type of subminiature *in vivo* transducer gives promise of eventually being sufficiently refined to constitute the simplest as well as the most flexible device for intralumen pressure registration.

Deranged motor activity of the gut is a common cause of distress but ordinary methods may not disclose the nature of the abnormality. Thus a new and sensitive method of studying digestive tract motility may provide a better understanding of some digestive disturbances. This concept is supported by our experience with a subject having an acute, mild gastritis following over indulgence in alcohol and excessive smoking approximately twelve hours preceding our studies. We recorded intralumen pressures (Fig. 2) from his gastroduodenal region while he was experiencing rhythmic, burning, mid-epigastric pain. The subject closed an electrical circuit during his periods of distress and thus recorded these intervals on the intraluminal pressure tracing. During the initial phase of this study the correlation between the subject's distress and the phasic pressure spikes was reasonably good. During the latter portion of the experiment, when the subject had trained himself to perceive his sensations more exactly, even better correlation was achieved. Several pressure spikes of approximately 95 cm. of water were recorded during this experiment. When the subject was free from gastritis, pressures of only 50 to 60 cm. were produced in the same region and the subject experienced no distress.

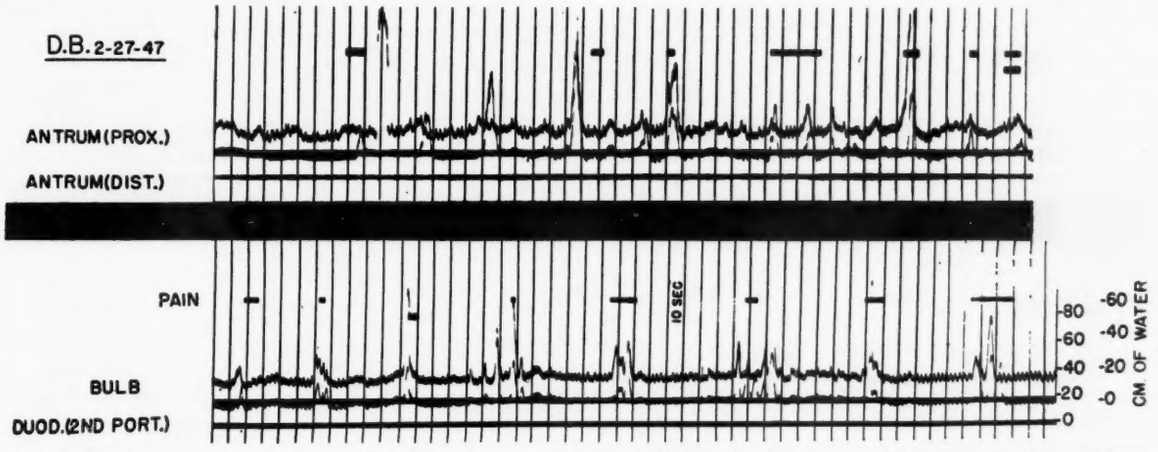

FIG. 2. Intralumen pressures recorded from the proximal and distal gastric antrum. The short horizontal bars indicate the intervals during which the subject experienced epigastric pain.

Vagotomy probably always produces some alteration in gastroduodenal activity, but these changes may at times be too minute for recognition by ordinary study methods. In two of our subjects shown by insulin and nocturnal secretion studies to be completely vagotomized, no roentgenologic evidence of depressed gastroduodenal motility was apparent. However, our pressure studies (Fig. 3) revealed almost complete absence of phasic pressure waves in this region.

The influence of gastrointestinal intralumen pressures on the translocation of contents has been extensively studied in relation to gastric

evacuation.[17] The open tube-optical manometer method was employed in humans and unanesthetized dogs to record accurately the pressures simultaneously from two portions of the gut about 18 mm. apart. The pressure was recorded from the extreme lower end of the pyloric antrum and from the first portion of the duodenum. Fluoroscopic observations were also made of the evacuation of a radio-opaque meal from the stomach. As a bolus began to pass through the pyloric sphincter, a key was closed and then reopened as the last of the bolus was evacuated. Thus a record showing the onset and termination of the bolus passage through the sphincter was recorded on the same photographic paper employed to record the intralumen pressures. Numerous studies of this type have shown that gastric evacuation follows a comparatively simple basic pattern.

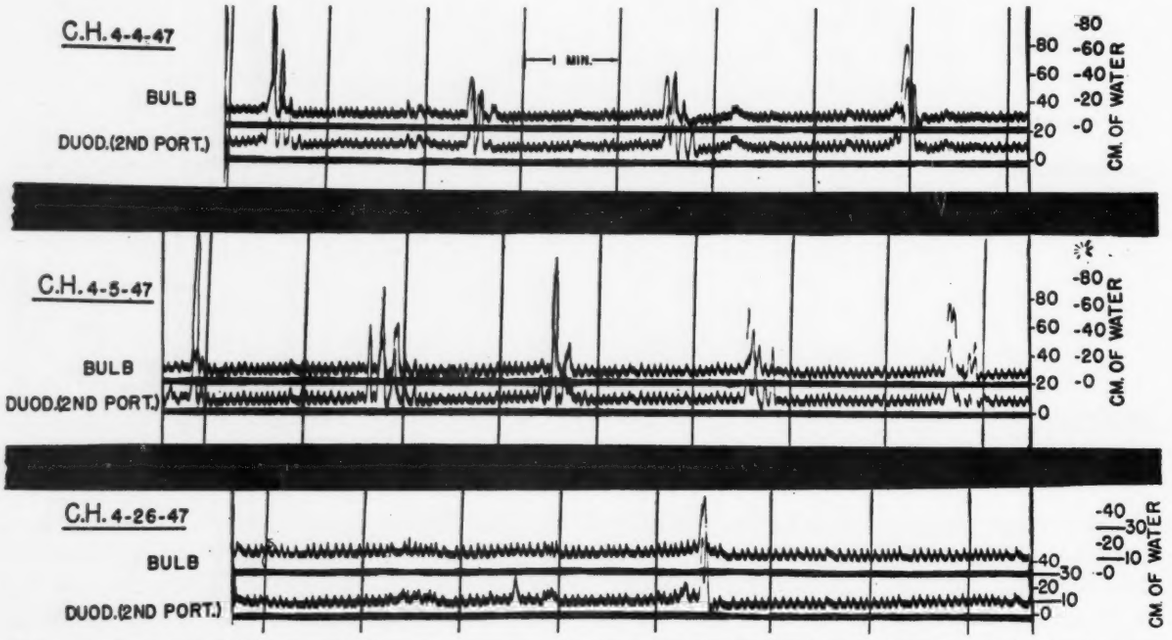

FIG. 3. Upper and middle records show the pressures developed in the first and second portion of the duodenum of a subject with peptic ulcer. Bottom record shows the pressures developed in the same regions of the subject following vagotomy performed on April 9, 1947.

With a subject in the horizontal position, an ingested meal collects in the gastric body and fundus under a comparatively constant pressure of 3 to 6 cm. of water. On this tonic or basal pressure weak rhythmic kneading and mixing contractions with their resultant low pressure spikes are superimposed at a rate of five to seven per minute. Periodically a portion of this material is squeezed into the pyloric antrum and is propelled by a peristaltic wave the entire length of the antrum to the sphincter in eight to twenty seconds. Deep cutting, progressive waves obviously propel the antral contents but even the more shallow waves which do not completely occlude the lumen elevate the pressure on the mass and cause it to move forward. On reaching the gastric side of the sphincter the bolus is under a pressure of 4 to 6 cm., the pressure on the duodenal side of the sphincter is 2 to 4 cm. and the sphincter is open. The resulting pressure gradient of 2 to 4 cm. causes the bolus to begin passing through the relaxed sphincter in "Gastric Evacuation Phase A." The pyloric sphincter now begins to contract and the last portion is evacuated during "Evacuation Phase B" despite the gradually increasing resistance offered by the sphincter. As the sphincter closure becomes more complete, the pressure in the terminal antrum rises sharply for the contents are acted upon proximally by the advancing antral wave and distally by the closing sphincter. Thus the pressure on the contents mounts to 20 or 30 cm. The proximal duodenum is still relaxed (receptive) and its intralumen pressure remains between 2 and 4 cm. The pressure gradient between antrum and duodenum, which rises from 2 to 28 cm. is sufficient to overcome the resistance offered by the sphincter and evacuate the last portion of

the bolus. Thus practically all of the chyme which approached the sphincter usually passes through during the cycle.

As the sphincter contraction reaches its peak, the first portion of the duodenum contracts, a pressure of 15 to 30 cm. is quickly established in this area and the contents are evacuated. Since the sphincter at this moment is entirely closed, the material cannot return to the antrum but is forced into a more distal portion of the duodenum, that is, into an area in which a lower pressure and a lower resistance to flow momentarily exists.

This cycle of propulsive peristaltic waves, associated pressure increases and establishment of pressure gradients continues rhythmically in the pyloric region until the stomach is entirely evacuated. Propulsion of material through the digestive tract is always dependent on intraluminal pressure gradients between immediately adjacent portions of the gut. The pattern of propulsive peristalsis, pressure gradient and translocation of material occurs through the entire tract in a manner similar to that which we observed in the pyloric region.

SUMMARY

The intraluminal pressures of the gut have been considered from several points of view.

The balloon-water manometer technic has been reviewed and its limitations for the accurate registration of pressures have been considered.

Several methods have been described which permit the accurate registration of the pressures developed in the digestive tract of man or animals.

The results of accurate intralumen pressure studies have been presented in regard to the normal values, and the pressures involved in gastric evacuation in normals and in patients with peptic ulcer, gastritis and following vagotomy.

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Clinico-pathologic Conference

Fever of Unknown Origin

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. M. (No. 206816), was a white married grocer, fifty-three years of age, who entered the Barnes Hospital for the first time on February 26, 1952, because of fever, malaise and anorexia of eight months' duration. The family history was non-contributory. The patient had enjoyed good general health. He had been a "heavy drinker" for many years and had smoked a moderate number of cigars.

During the summer of 1951 he noted the gradual onset of malaise, anorexia, fatigue and lethargy. These symptoms persisted and in August of that year he began to have shaking chills, night sweats and daily temperature elevations to 103° and 104°F. About September 1st he noted swelling of the right lower leg and foot. The involved area was painful and warm. He was admitted to another local hospital on September 21, 1951, where an excellent diagnostic study was performed. The pertinent physical findings included a temperature of 103°F., tachycardia and slight icterus. Laboratory studies revealed a red blood cell count of 2,730,000 with 9 gm. of hemoglobin. The white blood cell count was 9,700, the differential count showing 33 band forms, 51 segmented forms, 14 lymphocytes and 2 monocytes. The sedimentation rate was 32 mm. per hour. Urinalysis revealed 1+ albuminuria, 3+ glycosuria and 5 to 10 white blood cells per high power field in the centrifuged sediment. The urine was slightly positive for bilirubin, and the urine urobilinogen excretion was 21.6 mg. per twenty-four hours. The stool examination was negative. Two fasting blood sugars were 164 mg. per cent and 280 mg. per cent, respectively. The non-protein nitrogen was 30 mg. per cent, the total proteins 5.1 gm. per cent, with albumin 3 gm. per cent and globulin 2.1 gm. per cent. Agglutination tests against typhoid, paratyphoid, brucella and OX-19 antigens were negative. Cold agglutinins could not be demonstrated in the serum. Liver function tests were reported as follows: cephalin-cholesterol flocculation test, negative; thymol turbidity, 12.5 units; icterus index, 8 units; sodium bilirubinate, 0.6 mg. per cent; bilirubinglobin 2.2 mg. per cent.

Although the patient was treated with penicillin and streptomycin and given multiple blood transfusions, his fever persisted. Further laboratory data obtained on October 9, 1951, revealed a total protein of 6.4 gm. per cent with 2.5 gm. per cent albumin and 3.9 gm. per cent globulin. The cephalin-cholesterol flocculation test was 4+, the thymol turbidity 7.5 units. There was 39 per cent retention of bromsulphalein at forty-five minutes, the sodium bilirubinate was 1.5 mg. per cent and the bilirubinglobin 2.3 mg. per cent. Roentgenograms of the chest and a gastrointestinal x-ray series were said to have been negative.

The patient was then given terramycin, 500 mg. every three hours; this medication apparently controlled his temperature and he was discharged from the hospital and advised to continue taking terramycin. Subsequently, however, he did poorly. Fever, marked malaise and anemia reappeared, and the patient was again admitted to the outside hospital.

Because it was suspected that he might have a liver abscess, he was subjected to exploratory laparotomy on January 22, 1952. The liver was described as having "a fatty appearance." No abscess was seen. Subsequent to operation the patient did not do well. On the fourth postoperative day his white cell count was 51,300, the differential showing 3 myelocytes, 2 metamyelocytes, 31 band forms, 60 segmented forms, 3 lymphocytes and 1 monocyte. A bone marrow examination showed marked stimulation of neutrophilic elements and an increase in monocytes and monocytic-like cells. There was either a relative or absolute decrease in the erythroid elements; those present existed predominantly at the normoblastic level of matura-

tion. Megakaryocytes were present. No inclusion bodies were seen.

It was thought that terramycin might be responsible for the relative aplasia of the bone marrow and accordingly that drug was discontinued. Penicillin was reinstituted in a dose of 1 million units twice daily, but the patient's condition deteriorated progressively. Anorexia, nausea, vomiting, weakness, weight loss and difficulty in swallowing solid foods were all prominent complaints. During the month preceding admission to the Barnes Hospital he developed a cough productive of small quantities of mucopurulent sputum, but at no time did he have hemoptyses. During the period of hospitalization in the outside institution he received a total of eighteen blood transfusions; his red blood cell counts varied from 2,700,000 to 4,200,000, and the hemoglobin from 9 to 12.5 gm. Differential counts persistently exhibited a left shift. Blood cultures drawn on October 23 and 25, 1951, and on January 10, 1952, were reported as showing a gram-positive coccus identified as Staphylococcus albus. The organism was described as being resistant to penicillin, streptomycin and aureomycin, slightly sensitive to bacitracin and chloromycetin, and moderately sensitive to terramycin. The patient became irrational and was transferred to the Barnes Hospital for further study.

At the time of admission his temperature was 38.4°C., pulse 96, respirations 36 and blood pressure 80/40 mm. He was an emaciated, elderly white male who was acutely and chronically ill. Mild icterus was apparent. On the shoulder and right knee there were small erythematous petechial-like lesions. Examination of the eyes was entirely negative except for a patch of yellow exudate in the left fundus. The upper respiratory tract was normal. A few shotty anterior cervical lymph nodes were palpable, but there was no generalized lymphadenopathy. Examination of the chest revealed dullness at the right base posteriorly and laterally; breath sounds and tactile fremitus were diminished and a few fine cracking rales were heard. The heart was slightly enlarged to the left. The sounds were of fair quality and the rhythm was regular. A soft, grade II systolic murmur was heard over the entire precordium. Abdominal examination revealed a recent scar surrounded by several small ecchymoses. The liver was palpable 6 cm. below the right costal margin and was smooth and slightly tender. The spleen was palpable 6 cm. below the left costal margin and was smooth and hard.

The laboratory data were as follows: Blood counts: red cells, 4,050,000; hemoglobin, 11.5 gm.; white cells, 12,800; eosinophile count, 22 per cu. mm.; differential count: 80 segmented forms, 11 lymphocytes, and 9 monocytes; the red blood cells appeared slightly hypochromic. Reticulocytes, 3.4 per cent; platelet count, 85,000. Urinalysis: albumin, 1+; sugar, negative; sediment, negative; urobilinogen, negative; bilirubin, negative. Stool examination: negative. Cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 82 mg. per cent; blood sugar, 161 mg. per cent; sodium, 136.7 mEq./L; potassium, 3.2 mEq./L, CO_2 combining power, 26.6 mEq./L; chlorides, 117 mEq./L; total protein, 5.7 gm. per cent; albumin, 2.0 gm. per cent; globulin, 3.7 gm. per cent; alkaline phosphatase, 7 Bodansky units; sodium bilirubinate, 0.22 mg. per cent; bilirubinglobin, 1.12 mg. per cent; total bilirubin, 1.34 mg. per cent; cephalin-cholesterol flocculation test, 3+; zinc sulfate flocculation test, 3+; icterus index, 9 units; thymol turbidity, 1.3 units; prothrombin time, 58 per cent of normal. Coombs test, negative. Electrocardiogram: T waves isoelectric in leads I and II, and inverted in AVL and the precordial leads; S-T segments slightly depressed in leads V_1, V_2, V_3 and V_4. Roentgenogram of the chest: There were linear areas of scarring in the apices of both lungs. There was upward retraction and thickening of the accessory fissure on the right. Questionable shift of the mediastinum to the right was noted, and the right superior mediastinal nodes were enlarged. Both costophrenic angles were obliterated. The cardiac silhouette appeared to be within normal limits.

Shortly after the patient was admitted to the hospital a lumbar puncture was performed. The initial pressure was 180 mm. of water and the fluid contained only three cells. The protein was 35 mg. per cent, the colloidal gold curve was flat and the Wassermann test was negative. Cultures of the spinal fluid remained sterile. The patient was begun on therapy with norepinephrine in order to maintain his blood pressure. After a number of blood cultures were obtained penicillin in a dose of 300,000 units every three hours was started. In addition, streptomycin, 0.5 gm. every six hours, and terramycin, 0.5 gm. every three hours, were given.

On the day following admission the patient

was seen by a hematology consultant. Studies at that time revealed a red blood cell count of 4,460,000 with 11.7 gm. of hemoglobin; the white cell count was 12,250, the differential showing 78 segmented forms, 2 per cent band forms, 1 per cent eosinophiles, 14 per cent lymphocytes and 5 per cent monocytes. All polymorphonuclear leukocytes exhibited hypersegmentation and toxic vacuolization. The platelet count was 135,000 and the reticulocyte count 2.2 per cent. The bone marrow was cellular; numerous young megakaryocytes were seen. Immature plasma cells were more prominent in Wright's stained films. The bone marrow differential count was as follows: 42 per cent segmented forms, 12 per cent band forms, 12 per cent metamyelocytes, 8 per cent C myelocytes, 2 per cent basophiles, 2 per cent reticulum cells, 18 per cent primitive forms and 4 per cent plasma cells. There were 28 normoblasts, 5 late erythroblasts and 2 early erythroblasts per hundred white blood cells. Neither tumor cells nor cells containing histoplasma capsulatum were seen. The marrow was cultured for tubercule bacilli and for fungi.

On the second hospital day streptomycin was discontinued and tube feedings were instituted. That evening the patient's respirations rose to 40 and his pulse to 100. A transient gallop rhythm was audible but the lungs remained clear on auscultation. Oxygen was administered by nasal catheter and intravenous aminophyllin was given. Increasing amounts of norepinephrine were required to maintain the patient's blood pressure at satisfactory levels.

Early on the morning of the third hospital day, February 28, 1952, he became comatose. His blood pressure fell to 50/0, the pulse rose to 160, the respirations to 50 and the temperature to 40.2°C. The lungs remained clear. An electrocardiogram revealed supraventricular tachycardia with prolonged intraventricular conduction. Despite increasing amounts of norepinephrine, intravenous adrenocortical extract, intramuscular cortisone, intravenous sodium salicylate and 1.6 mg. of lanatoside C,® the patient failed to respond. He became more cyanotic, his blood pressure became unobtainable, his temperature rose to 40.7°C. and he expired. At the time of his death the blood cultures were sterile.

CLINICAL DISCUSSION

DR. CARL V. MOORE: This man had been ill for approximately eight months. During that period he had fever, anorexia and moderate jaundice. The findings suggested involvement of the lungs, liver, spleen, lymph nodes and possibly the bone marrow. In addition, the patient probably had mild diabetes. Prior to his death no definitive diagnosis was established; it is quite obvious that the physicians who were taking care of him faced a most difficult problem. It may well be equally difficult for us to make the correct diagnosis. By way of beginning, I should like to ask Dr. Wilson to comment on the various roentgenographic examinations. The films from the outside hospital were made available to him; and although the report in the protocol suggests that the first chest film was negative, I believe on review here a different interpretation was made.

DR. HUGH M. WILSON: The chest film taken in the outside hospital on September 22, 1951, was suggestive of cardiac enlargement, primarily left ventricular in type. There was no definite hilar node enlargement, but numerous 2 to 3 mm., tubercle-like lesions were noted throughout both lung fields. Several weeks later another chest film showed essentially the same findings. The gastrointestinal series was interpreted as negative, and we would agree except to mention that enlargement of the liver and spleen was demonstrable in those films. When the patient was readmitted to the outside hospital after the first of the year, another chest film was obtained which again showed cardiac enlargement and the same discrete focal areas mentioned previously. The chest film made after the patient was transferred to the Barnes Hospital was nonstandard because of his critical condition. Nonetheless, several interesting findings were apparent. First, the patient had obviously lost a significant amount of weight as indicated by the striking decrease in subcutaneous tissue. This decrease could not be explained on the basis of the different technic of the films *per se*. Second, there was suggestive deviation of the mediastinal contents to the right. Third, definite thickening in the interlobar fissure was present, and fourth, the right hilar nodes were enlarged. Taken as a whole the roentgenologic findings are compatible with a granulomatous lesion, possibly histoplasmosis.

DR. MOORE: Thank you, Dr. Wilson. Dr. Wood, can you suggest a diagnosis which would explain all the clinical manifestations presented by this patient?

DR. W. BARRY WOOD, JR.: First of all, I

would agree with your statement that this case constitutes a most difficult problem. Dr. Wilson has already suggested that this patient may have had one of the granulomas, a suggestion with which I concur. In general the findings were compatible with that group of diseases—one would include tuberculosis, brucellosis, and histoplasmosis as well as non-infectious granulomas such as Hodgkin's disease and Boeck's sarcoid.

DR. MOORE: Those certainly are among the most common ones. Do you think that any of the data available enable one to differentiate between the infectious and non-infectious types?

DR. WOOD: No, I do not. Since Hodgkin's disease can simulate chronic infection, I do not believe that it can be ruled out on the information available. Among the infectious granulomas, the negative brucella agglutination helps to exclude that diagnosis. Jaundice is also rather unusual in brucellosis. Certainly tuberculosis merits serious consideration although no confirmatory laboratory results were forthcoming.

DR. MOORE: Dr. Harford, do you agree that the negative agglutination for brucellosis constitutes reasonably good evidence against that diagnosis. You will remember that Eisele at the University of Chicago reported an interesting study of nineteen patients with bacteriologically proven brucellosis.[1] He sent sera from this group of patients to various clinical laboratories and also performed agglutination tests in his own laboratories employing a number of brucella antigen preparations. When all the results were totaled, positive and negative agglutinations with various antigens were reported for each of the nineteen cases. Doesn't Eisele's study suggest that caution be exercised in ruling out brucellosis on the basis of a single negative agglutination?

DR. CARL HARFORD: As I remember that study, there was a tremendous variation in the results. I think it is reasonable to say that a single negative agglutination test is evidence against brucellosis. There have been rare instances, however, in which patients with positive blood cultures have been reported to have negative agglutinations.

DR. MOORE: As further evidence against brucellosis in this case, of course, can be added the fact that the patient failed to respond to a number of antibiotics which should have been effective had he had brucellosis.

DR. HARFORD: That is an important point.

DR. MOORE: Let us now consider this patient's cardiac manifestations. Would you comment on them, Dr. Massie?

DR. EDWARD MASSIE: This patient actually had no serious symptoms referable to his heart until his terminal episode. When he entered the Barnes Hospital, he was described as having a grade II systolic murmur over the precordium; but in view of the fact that he had considerable fever at the time, it is possible that the murmur was hemic in origin. The electrocardiograms could be interpreted in one of two ways. They are compatible with anterior myocardial ischemia as evidenced by the inverted T waves in the V leads. On the other hand, the S-T segments were slightly depressed in leads V_1, V_2, V_3 and V_4. Such a change can be taken as evidence of right ventricular strain and thus indirectly of pulmonary disease, possibly of pulmonary infarction. I would favor the second explanation; that is, that the electrocardiographic changes were secondary rather than indicative of primary coronary artery disease *per se*. The patient also had a supraventricular tachycardia terminally, but I do not believe that one can attribute such an arrythmia to a specific cardiac lesion in a dying patient. The only question which I would like to raise concerns the reported positive blood cultures in October, 1951, and January, 1952. Although Staphylococcus albus is not an uncommon contaminant, the fact that three cultures were positive for the same organism is impressive, particularly when one recalls that the patient also had fever, malaise, anorexia, weight loss and a murmur. Certainly the diagnosis of bacterial endocarditis must be mentioned.

DR. MOORE: Your suggestion is an excellent one, Dr. Massie. Returning, however, to the possibility that this patient was suffering from a diffuse granulomatous disease, infectious or non-infectious, Dr. Reinhard, what are the criteria upon which the diagnosis is based?

DR. EDWARD H. REINHARD: Fever, splenomegaly and hepatomegaly are important clinical features of this group of diseases, and anemia, leukocytosis and a left shift in the differential count are common; the bone marrow frequently shows an increase in reticulum cells without

[1] EISELE, C., MCCULLOUGH, N. B. and BEAL, G. A. Discrepancies in the agglutination test for brucellosis as performed with various antigens and as reported from different laboratories. *J. Lab. & Clin. Med.*, 32: 847, 1947.

other diagnostic changes. Hyperglobulinemia is another feature. The findings in this case, in my opinion, are certainly compatible with one of the granulomas.

DR. MOORE: Do you favor an infectious or a non-infectious type?

DR. REINHARD: Although I don't believe Hodgkin's disease can be ruled out, I think the patient had an infection.

DR. MOORE: Dr. Goldman, you have had an opportunity to review the chest x-rays. Would you comment on your interpretation of the films?

DR. GOLDMAN: The changes were not specific but in my opinion were not typical of tuberculosis or of histoplasmosis, especially in view of the fact that there was some clearing on the final film. On the other hand, the combination of pulmonary infiltration with fever, splenomegaly and hepatomegaly makes histoplasmosis or tuberculosis important possibilities.

DR. MOORE: Several years ago, Dr. Wood, you took care of a patient with nocardia endocarditis. Should nocardia infection be considered here?

DR. WOOD: Although nocardia infection may produce a clinical picture similar to that which characterizes the granulomas as a group, it is extremely rare. The patient whom we saw here several years ago with nocardia endocarditis fortunately responded to therapy with multiple antibiotics. Our experience with nocardial infections is too limited to do more than mention them in passing.

DR. MOORE: Of other fungus infections, blastomycosis is unlikely because it seldom involves the liver and spleen so extensively. Coccidioidomycosis is rare in this part of the country and probably would not explain all of the findings. By a process of elimination histoplasmosis seems to me to be the most likely diagnosis. On the other hand, as has been pointed out, certain non-infectious lesions, especially those of Hodgkin's disease, certainly are important possibilities and cannot be excluded.

DR. ALBERT I. MENDELOFF: Some of us have wondered whether two diagnoses rather than one should be made. On the basis of the liver function tests, I do not believe that one could differentiate between primary liver disease or a generalized granulomatous disease.

DR. MOORE: Unfortunately, a liver biopsy was not obtained when the exploratory laparotomy was performed in the other hospital. It might have provided an answer to the problem. Are there any other diagnostic suggestions?

DR. WOOD: One point in the history has not been touched upon; namely, that earlier in this patient's illness he noted swelling of the right leg and foot with localized pain and heat. Perhaps this involvement was due to staphylococcal infection which was complicated by thrombophlebitis and multiple septic infarcts in the lungs. Dr. Massie has already suggested staphylococcal endocarditis; chronic staphylococcal septicemia, with or without endocarditis must be considered.

DR. MOORE: Dr. Goldman, if this patient had phlebothrombosis as Dr. Wood suggests, could it have been an accompanying feature of histoplasmosis *per se?*

DR. GOLDMAN: In my experience it is not common in histoplasmosis.

DR. MOORE: It is of interest that Furcolow encountered several instances of thrombotic complications in a series of sixteen or seventeen patients with histoplasmosis. Whether or not the thromboses were related to the disease or were incidental is not known.

DR. MASSIE: I would like to emphasize that multiple pulmonary infarcts, possibly septic in character, are quite compatible with the electrocardiographic changes.

DR. MOORE: Dr. Daughaday, do you think that this patient had adrenal insufficiency?

DR. WILLIAM H. DAUGHADAY: A striking proportion of patients with histoplasmosis has presented the symptoms of adrenal insufficiency, due to destruction of the cortex by the organism. In this particular case, although certain features suggest the diagnosis of Addison's disease, I do not believe that one would be justified in making that diagnosis. The high fasting blood sugars are against it.

DR. MOORE: In summary, I believe that the consensus favors the diagnosis of a chronic granuloma, probably infectious. Histoplasmosis is a likely possibility. Staphylococcal septicemia with pulmonary infarcts, possibly in association with endocarditis, has also been mentioned.

Clinical Diagnoses: ? Histoplasmosis; ? staphylococcal septicemia, with or without endocarditis.

PATHOLOGIC DISCUSSION

DR. MICHAEL MCNALLEY: At autopsy the lungs weighed 1,400 gm. The dark red, cut

surfaces exuded a large quantity of thin fluid. In every lobe a number of thin-walled abscesses was present, ranging in size from 1 cm. to 5 cm. in diameter; pneumonia did not involve the intervening parenchyma. The pleurae were covered by a thin exudate of fibrin, and there were 300 cc. of yellow fluid in the right pleural space. The heart was enlarged to 420 gm. A large friable vegetation 2½ cm. long and 1 cm. broad covered the medical leaflet of the tricuspid valve. On the endocardium of the right ventricle below the valve there were multiple small flat parietal vegetations several millimeters in diameter. The other valves of the heart showed no significant evidence of deformity or chronic endocarditis. The liver weighed 2,540 gm. and showed signs of chronic passive congestion with an additional slight rust color. The spleen was quite large and hyperplastic. A small amount of ascitic fluid and absence of the yellow color of lipoid in the adrenal cortex were the only other gross lesions relative to the clinical history.

Dr. David E. Smith: Figure 1 illustrates a rather low magnification of a slide from the vegetation on the tricuspid valve. At this power complete obliteration of the tissue of the normal valve was apparent and there were large, dark, sharply outlined masses beneath an accumulation of acellular fibrin. Figure 2 is a view of the dark masses through the oil immersion lens and shows them to be colonies of cocci. Cultures of this vegetation, the abscesses in the lungs and the blood postmortem yielded a nonhemolytic Staphylococcus aureus that was coagulase and mannite positive and corresponded exactly to an organism that ultimately grew out in the blood cultures taken during life. These latter cultures contained no visible growth at the end of the usual period of incubation but were saved for special attention because of the findings at autopsy. Bacteria from all sources showed almost identically high resistance to penicillin, bacitracin and chloramphenicol and slight sensitivity to aureomycin and terramycin. It was probably the same strain of organism that had been isolated three times prior to the patient's last admission.

The vegetation on the tricuspid valve showed histologic evidence of a subacute nature; Figure 3 shows the cellular proliferation and fibrous thickening that had occurred at the base of the valve about the zone of completely necrotic material under the vegetation. On the right side of the illustration there is a focus of particularly marked endothelial proliferation. This histologic evidence as well as the clinical history made the nature of the causal organism a little surprising, since staphylococcus is generally stated to cause acute bacterial endocarditis. Part of this modified picture might obviously have been due to the effect of the antibiotics administered.

Figure 4 is from the edge of one of the abscesses in the lung. Although the walls were thin, they were well organized fibrous tissue and contained many dilated small capillaries typical of an organizing pyogenic membrane. Of course, the usual lining of fibrin and necrotic material surrounded the central cavity although that is not shown here. These abscesses were of a sufficiently chronic histologic nature to be compatible with the history of the roentgenologic discovery of pulmonary infiltration on several examinations.

Figure 5 is of a slide of a lymph node; it is typical of all the lymphoid tissue examined. The large number of plasma cells were particularly prominent. This was compatible with the observations made during life on the bone marrow; and, knowing now of the bacterial endocarditis which must have been present for all of this man's history, we can interpret these cells as evidence of chronic antigenic reaction to the inflammation. The spleen itself showed the same picture of hyperplasia with plasma cells. A section of the liver in Figure 6 showed a marked thickening of the fibrous tissue around the central vein, some atrophy of the hepatic cords, and the extension of strands of fibrous tissue along the sinusoidal basement membranes and between the portal spaces and the central veins. These were histologic lesions of cardiac or congestive cirrhosis. It was somewhat perplexing that the clinical history recounted no previous episodes of cardiac failure and there was so little other evidence of systemic edema or congestion. There remained, nevertheless, no other explanation of the enlarged liver other than the lesion of the tricuspid valve that undoubtedly interfered with its efficient action.

Vegetative endocarditis due to staphylococcus is uncommon, but it is rather remarkable that it frequently involves the tricuspid valve and is the most common cause of bacterial endocarditis on that valve. In 9,000 autopsies from our department Dr. Margaret G. Smith found

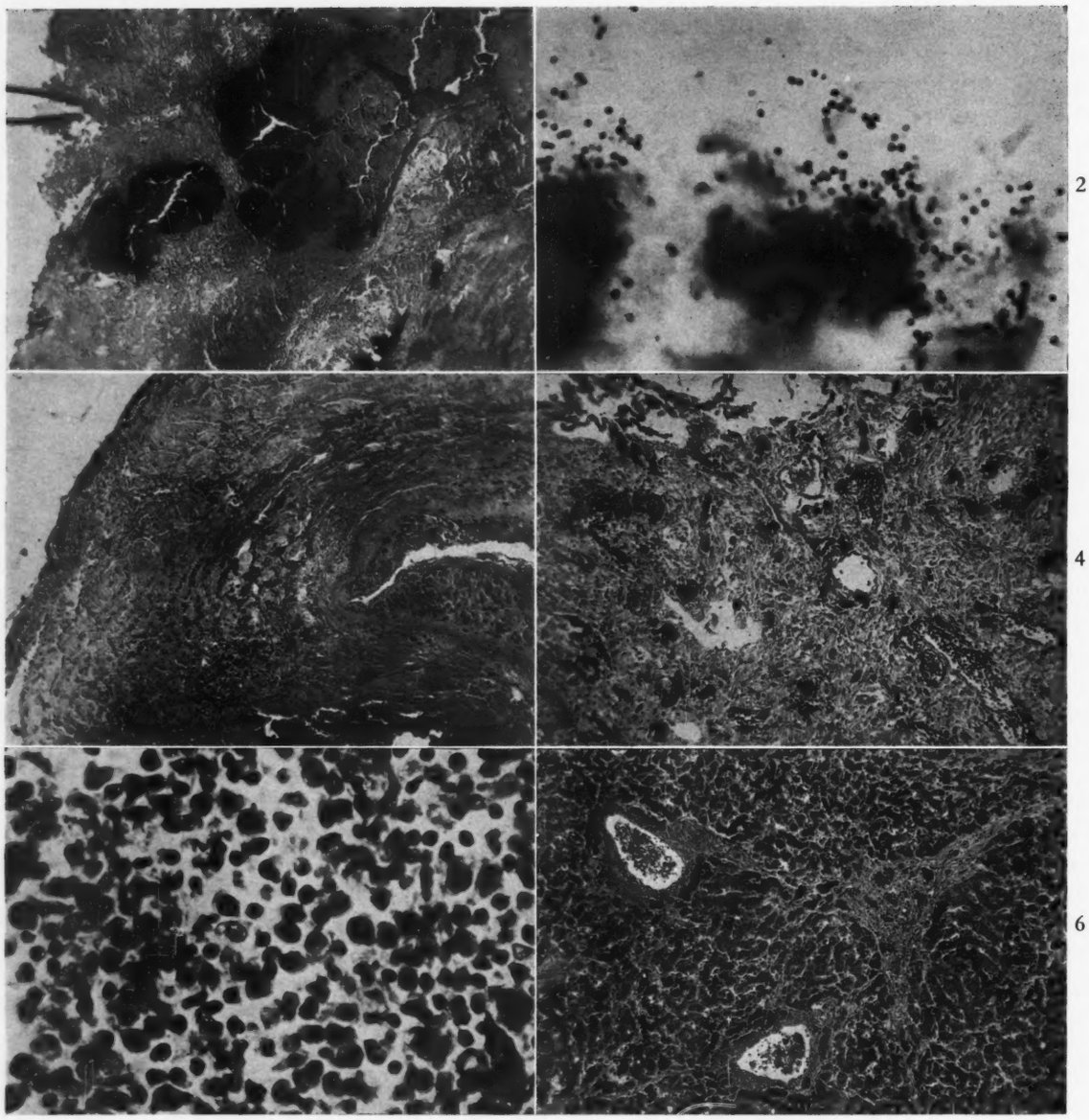

FIG. 1. The vegetation on the tricuspid valve; the fibrinous surface in the upper left corner overlies black masses of bacterial colonies and total necrosis of the valve leaflet.

FIG. 2. The colonies of cocci on the vegetation; by culture these organisms were identified as Micrococcus pyogenes var. aureus.

FIG. 3. The base of the tricuspid leaflet showing subacute cellular infiltration, fibrosis and endothelial proliferation.

FIG. 4. Organized pyogenic membrane in the outer portion of the wall of one of the abscesses in the lung.

FIG. 5. A greatly increased number of plasma cells in a typical lymph node. These cells were part of the immunologic reaction to the infection and were seen in the lymph nodes, spleen and bone marrow.

FIG. 6. Increased fibrous tissue about central veins, portal spaces and along the sinusoidal basement membranes in the liver, typical of congestive cirrhosis.

twenty cases of staphylococcal endocarditis, six of which had vegetations only on the tricuspid valve; two additional cases showed involvement of both the tricuspid and mitral valve. Streptococcus viridans was the only other organism responsible for more than one case of tricuspid endocarditis and it involved the tricuspid valve alone in only 1 of 8 cases.

Demonstration of the lesions of so-called "right-sided bacterial endocarditis" clarified most of the features in this case. The syndrome has been well described by Blumgart,[2] Barker[3] and others and is, of course, characterized by the presence of embolic lesions in the lungs and the absence of the peripheral embolic phenomena usually seen in cases of subacute bacterial endocarditis. In this case the pulmonary abscesses showed the direct effect of such infected emboli. The other viscera showed only the congestive cirrhosis in the liver, presumably due to the disarranged tricuspid valve, and such secondary lesions as hyperplasia of the spleen, hemosiderosis of the liver and spleen and lipoid depletion of the adrenal cortex.

[2] BLUMGART, H. L. The clinical syndrome of subacute bacterial endocarditis involving the right chambers of the heart. *M. Clin. North America*, 16: 881–893, 1933.

[3] BARKER, P. S. A clinical study of subacute bacterial infection confined to the right side of the heart or the pulmonary artery. *Am. Heart J.*, 37: 1054–1068, 1949.

DR. MARVIN ROSEGAN: How should one treat such patient with an infection due to a resistant staphylococcus?

DR. WOOD: This case illustrates a point worth emphasizing; namely, that it is the staphylococcus which is the organism which at present is most often found to be resistant to antibiotics. Further, the incidence of resistant staphylococci is apparently increasing all the time. It is extremely difficult to treat patients such as the one in this case even if one knows exactly what he is dealing with. I probably would have given the highest possible doses of the drugs most likely to kill the organism, perhaps 20 or 25 million units of penicillin per day and streptomycin in a dose of 2 gm. a day.

Final Anatomic Diagnoses: Subacute bacterial endocarditis of the medial leaflet of the tricuspid valve (Micrococcus pyogenes, var. aureus, isolated by culture); multiple abscesses in all lobes of the lungs; chronic passive congestion with central lobular fibrosis in the liver.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

Research Society Abstracts

The Western Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE FIFTH ANNUAL MEETING, CARMEL, CALIFORNIA, JANUARY 25 AND 26, 1952

FRUCTOLYSIS INDEX IN NORMAL AND ABNORMAL HUMAN SEMINAL FLUID. *A. R. Abarbanel,** College of Medical Evangelists, Los Angeles, Calif.

Seminal plasma is unique among body fluids for its high content of fructose. Human seminal fluid obtained under standard conditions has been evaluated under various circumstances. Over 100 men and several hundred samples have been studied.

First a standard utilization curve or fructolysis index was established by noting in the semen of men of proven fertility the utilization of fructose by spermatozoa over a three- to six-hour period at hourly intervals. Fructolysis indices were also established in the semen of men in oligozoospermia, necrozoospermia, azoospermia, hemozoospermia, pyozoospermia, oligospermia and hyperspermia. The effect of various endocrine substances upon the fructoloysis index has also been determined. In addition, correlation studies have been made of percentage motility and viability (using the live-dead stain of Blom) and the fructolysis index.

From these studies it is believed that the fructolysis index may prove to be a valuable guide in assessing the fertility potential of human semen and its contained spermatozoa.

PTC-FACTOR DEFICIENCY: A PREVIOUSLY UNDESCRIBED HEMOPHILIA-LIKE DISEASE DUE TO DEFICIENCY OF A HERETOFORE UNKNOWN PLASMA THROMBOPLASTIN COMPONENT. *Paul M. Aggeler,** *Sidney G. White, Mary Beth Glendening, Ernest Page,** *Tillie B. Leake and George Bates,* Divisions of Medicine, Obstetrics and Gynecology, and Pediatrics, University of California School of Medicine, San Francisco, Calif.

Hemophilia was excluded in a fifteen year old male with a markedly prolonged whole blood-clotting time and hemorrhagic diathesis by the following: Patient's and hemophilic plasma mutually corrected each other's defects; potent anti-hemophilic globulin (Cohn's Fraction I) was ineffective; barium sulfate adsorbed plasma was active against hemophilia but inert in this case. Anticoagulants were excluded because of the effectiveness of small amounts of normal plasma *in vivo* and *in vitro*. Known platelet factors were excluded by "specific" tests for accelerator and thromboplastin content of platelets; centrifuged-induced "platelet-free" normal and hemophilic plasmas and Berkfelded normal plasma were as effective as platelet-rich specimens. Known prothrombin accelerators were excluded by normal tests for labile-factor and plasma-accelerator globulin, and normal one- and two-stage prothrombin times. The effectiveness of "dicumarol plasma" excluded the "stable" prothrombin accelerators reported to be affected by dicumarol.

Characterization of the deficient factor as a plasma thromboplastin component (PTC) is shown by the following: Patient's abnormal two-stage prothrombin consumption test was corrected by small amounts of plasma *in vivo* and *in vitro;* a minimal effective concentration of tissue thromboplastin was equally effective on the patient's plasma and hemophilic plasma.

Preliminary steps toward isolation of PTC show that it can be adsorbed from normal, hemophiliac and "dicumarol" plasmas by barium sulfate and eluted with sodium citrate; it can be passed through a Berkefeld but not a Seitz filter; it is associated with the plasma euglobulins but is distinct from the anti-hemophilic globulin contained in Cohn's Fraction I.

GLUCOSE METABOLISM IN THE RED BLOOD CELL. *Grant R. Bartlett and Arthur A. Marlow,** Scripps Metabolic Clinic, La Jolla, Calif.

The mature non-nucleated mammalian erythrocyte can be considered a living cell whose life is dependent on a continuous energy supply derived from the anaerobic splitting of glucose to lactic acid. A rational approach to problems concerning *in vitro* blood storage and the many blood dyscrasias of unknown etiology must include investigation of the intimate details of glucose degradation.

We have incubated human blood *in vitro* with

* Asterisk indicates member of the Society; those not so indicated are by invitation.

radioactive carbon tagged glucose for periods giving approximately 50 per cent conversion of sugar to lactic acid. Although only net glucose disappearance and equivalent lactic acid formation are apparent, many water-soluble, small-molecule components of the cell become radioactive. The compounds labeled and their level of activity provide both a qualitative and quantitative picture of the metabolic route traversed by glucose carbon. The following substances, fractionated from trichloracetic extracts of red cells, showed significant radioactivity and therefore were intermediates in the path of red cell glycolysis: glucose-1-phosphate, glucose-6-phosphate, fructose-6-phosphate, triose-phosphate, diphosphoglycerate, hydroxyacetic-phosphate, ribose-phosphate, adenylic acid, pyridine-nucleotide and at least two unidentified materials. The rapid labeling of ribose necessitates an amendment to current concepts of glycolysis. Of special interest was the high activity of the unique red cell compound, 2,3-di-phosphoglycerate.

METABOLIC INTERRELATIONSHIPS BETWEEN ACTH AND POTASSIUM. *Leslie L. Bennett, Grant W. Liddle and Richard C. Bentinck*, Metabolic Laboratory and the Divisions of Physiology and Medicine, University of California School of Medicine, Berkeley and San Francisco, Calif.

It has been shown previously that feeding a diet high in potassium chloride prevents ACTH-induced nitrogen loss in rats and diminishes ACTH-induced glycosuria in partially depancreatized rats. This is a report of studies to determine how potassium might modify effects of ACTH in human subjects. Four arthritic patients were studied on a metabolic balance regimen and large doses of potassium salts (up to 36 gm. of potassium acetate per day) were administered both with and without simultaneous ACTH therapy.

Potassium in large doses administered concurrently with ACTH to arthritic patients fails to modify the anti-rheumatic and "nitrogen-wasting" effects of ACTH. Other effects of ACTH which are not modified by potassium include uric acid diuresis, eosinopenia, rise in fasting blood sugar and rise in 17-ketosteroid excretion.

On the other hand, the effects of ACTH upon electrolyte metabolism are definitely modified by potassium. The sodium retention which consistently occurs when ACTH therapy is initiated is prevented or diminished by the concurrent administration of potassium. Superimposing potassium therapy upon an already established ACTH regimen induces prompt and marked diuresis of sodium. The marked sodium diuresis which ordinarily follows withdrawal of ACTH therapy may not occur in patients who have received potassium concurrently with ACTH. Potassium, therefore, inhibits the sodium-retaining effects of ACTH.

Although potassium administration may minimize the hypokalemia due to acute administration of ACTH, the serious depletion of potassium which may result from prolonged treatment with ACTH can be repaired only with difficulty while ACTH treatment is continued.

VASOMOTOR REACTIONS OF VISCERAL ARTERIES TO EPINEPHRINE. *Howard R. Bierman,* Ralph L. Byron, Jr., Rutherford Gilfillan, Keith H. Kelly and Laurens White*, Laboratory of Experimental Oncology, the Division of Medicine, University of California School of Medicine, San Francisco, Calif.

By intra-arterial catheterization of the liver, kidney, spleen and lung, and with rapid arteriographic technics, it has been possible to observe the vascular patterns of these viscera in man. The introduction of various concentrations of epinephrine and its derivations produces specific changes in the vascular pattern of these organs.

In general, the more rapid administration and the larger doses exerted more profound effects. In the spleen and liver, at uniform rates of administration, doses of 0.5 to 0.1 mg. of epinephrine causes the disappearance of small vessel pattern. Between 0.1 to 0.2 mg. the major arteries show diminution of caliber. Doses above 0.2 mg. cause complete spasm of the splenic artery with marked contraction of the hepatic artery. Renal and pulmonary arteries vary in their vasoconstrictor responses to the aforementioned concentrations.

MECHANISMS OF DEGLUTITION, WITH REFERENCE TO DISABILITY IN PATIENTS HAVING BULBAR-PHARYNGEAL POLIOMYELITIS. *James F. Bosma (introduced by Vincent C. Kelley)*, Department of Pediatrics, University of Utah, Salt Lake City, Utah.

The critical factor in the disability of deglutition in patients having bulbar-pharyngeal poliomyelitis is that of weakness of the pharyngeal constrictor musculature. Evaluation of this weakness is made difficult by its common association with weakness of the levator veli

palatini muscle, which causes apparent disability of the ipsilateral oropharynx. Distinction of actual from seeming weakness of the constrictor musculature is made by evaluation of transverse movement of the posterior pharyngeal wall.

The role of the levator and constrictor muscles in function of the pharynx has been demonstrated in comparative dissection studies of cadavers and cinema studies of patients having the pharynx exposed by maxillofacial surgery. The various patterns of paralytic disability of the pharynx in bulbar poliomyelitis have been studied by cinematography and by serial radiographic studies.

PITUITARY ADRENOCORTICAL SYSTEM IN PANCREATIC HYPERINSULINISM. *Harold Brown (introduced by F. H. Tyler)*, Department of Medicine, Veterans Administration Hospital and the University of Utah College of Medicine, Salt Lake City, Utah.

A fifty-eight year old man with severe hypoglycemia of eight years' duration which was due to an islet cell adenoma of the pancreas was successfully treated with ACTH and cortisone prior to operation.

The results of oral and intravenous glucose tolerance tests, insulin and epinephrine tests during the control, treatment and postoperative periods are reported. A nitrogen balance study during cortisone therapy indicated that the correction of hypoglycemia could not be attributed to the protein catabolic effect of cortisone but was due, presumably, to an anti-insulin effect in the tissues.

It is postulated that even though exogenous hypercorticism can correct the hypoglycemia of hyperinsulinism, the potent stress of the hypoglycemia cannot induce persistent endogenous hypercorticism because of the self-regulating mechanism of the pituitary adrenocortical system. If persistent endogenous hypercorticism did develop, it would be detrimental to other body systems.

URINARY CHROMOGENS IN ACUTE PORPHYRIA. *K. B. Davison and R. A. Aldrich (introduced by Arthur Seaman)*, Departments of Biochemistry, Pediatrics, and the Division of Clinical Pathology, University of Oregon Medical School, Portland, Ore.

The urine of patients suffering from an attack of acute porphyria contains a number of substances including uroporphyrin which are probably the result of the disturbed pyrrole metabolism in this disease. One of these substances is an Ehrlich reacting chromogen which Waldenström originally described. Many believe that this substance, designated porphobilinogen, is closely related to the toxicity of the disease and consequently is of more pathologic importance than the uroporphyrin. Porphobilinogen has never been entirely purified although several investigators have contributed to our knowledge of its properties. Waldenström and others believe that the substance may form either uroporphyrin or a dark brown pigment, porphobilin. This dual role depends on the conditions under which the conversion occurs.

The presence of a colorless chromogen for coproporphyrin in the urine has been proved beyond doubt. It appears in normal, porphyria and other pathologic urines. Thus there is reason to speculate on the existence of a similar chromogen for uroporphyrin in porphyria which could account for the dual behavior of the so far incompletely purified porphobilinogen. In short, porphobilinogen could be two or more substances.

Sveinsson et al. have provided a technic by which all preformed porphyrin may be quantitatively removed from porphyric urine, leaving the residual urine with a strong porphobilinogen test. We have made a study of urine from a case of acute porphyria using this technic. Evidence will be presented which may be interpreted to indicate that there is a chromogen of uroporphyrin in this residual prophyrin-free urine and that it is separable from the Ehrlich reacting substance.

OBSERVATIONS ON THE NATURE OF THE "STORAGE LESION" IN PRESERVED BLOOD. *C. A. Finch,* B. W. Gabrio and A. R. Stevens*, Department of Medicine, University of Washington School of Medicine, Seattle, Wash.

Satisfactory preservation of blood for three weeks has been possible at 4°C. using an acidified citrate-glucose media. Characteristic structural and biochemical changes in the erythrocyte have been described during storage.

Because of the critical role that glucose plays in erythrocyte preservation, particular attention in *in vitro* studies has been directed at the carbohydrate metabolism of the erythrocyte. *In vivo* measurements of cell survival have been made using erythrocytes tagged with radioiron in animals and by the differential agglutination technic in man. Changes occurring during normal cell aging *in vivo* have been compared

with those found during storage. The effect of cell age on post-transfusion survival of stored blood has been determined during tagged erythrocytes. It is concluded that the storage changes are not related to cell senescence as it occurs *in vivo*.

It has been possible to demonstrate that abnormalities in carbohydrate metabolism of the stored cell are reversible after transfusing in animals and man. Plasma replacement *in vitro* has much less effect. Survival studies indicate that a change of plasma has no definite effect on survival but that "rejuvenation" of stored cells by placing them in the circulation of another animal for a short time may ameliorate storage damage.

EVALUATION OF OPERATIVE RISK IN THE PRESENCE OF LIVER DISEASE. *Arthur B. French (introduced by John Waldo)*, Department of Medicine, Massachusetts General Hospital and Departments of Medicine and Radiobiology, University of Utah College of Medicine, Salt Lake City, Utah.

In order to evaluate better the risk of operation in the patient with liver disease, pre- and postoperative data on seventy patients subjected to operations for the relief of portal hypertension were analyzed. Most of these were splenorenal or portacaval shunts but some were emergency procedures such as splenic artery or esophageal vein ligations. Operative risk was judged by the operative mortality associated with the presence of various signs, e.g., jaundice (37 per cent), ascites (55 per cent), spider angioma (41 per cent). In the absence of these signs operative mortality has ranged from 10 to 16 per cent. Other factors, particularly the patient's nutritional status, cannot be measured statistically but undoubtedly affect the operative risk greatly.

Of the laboratory data, serum albumin level seemed the most significant. With rising albumin levels the operative mortality dropped from 100 per cent (albumin below 3.0 gm. per 100 cc.) to no mortality in the patients with albumin levels above 4.5 gm. Total protein and globulin levels were much less significant. Bromsulfalein retention and serum bilirubin also showed increasing mortality with increasing abnormality. It was striking that no deaths occurred in patients with cephalin flocculations less than 3+. Phosphatase and prothrombin values were not correlated well with operative mortality in spite of the fact that over half the deaths were due to bleeding from the operative site with failure of coagulation of the blood. Liver biopsies in the fatal cases rather consistently showed a postnecrotic type of cirrhosis with poor regeneration of the liver cells and heavy bands of fibrous tissue.

STUDIES ON DIURNAL VARIATION IN STEROID EXCRETION IN PATIENTS WITH CONGESTIVE HEART FAILURE AND CIRRHOSIS OF THE LIVER WITH ASCITES. *Ralph Goldman and Samuel H. Bassett,** Metabolic Unit, Veterans Administration Center, and Department of Medicine, University of California, Los Angeles, Calif.

Recent studies have indicated that there is frequently a nocturnal diuresis of water and sodium in patients with cardiac failure and cirrhosis of the liver with ascites. A similar alteration has not been so uniformly observed in the pattern of excretion of potassium and creatinine. Studies of the diurnal variation of creatinine and inulin clearances, as well as other data obtained by sodium load experiments, fail to establish that this phenomenon can be explained by renal hemodynamics alone.

To determine the role of adrenal hormones in producing these alterations by affecting tubular reabsorption of sodium a study was made of the diurnal variations in the excretion of lipid soluble reducing steroids. Other workers have previously established that there is a morning increase in excretion of these steroids which exceeds the morning increase in glomerular filtration rate. This finding was confirmed. However, in those patients with cardiac failure and cirrhosis in whom nocturia was present it was found that there was also a nocturnal increase in steroid excretion. This did not appear to be related to stress, since the total steroid excretion was not increased, but did parallel changes in creatinine excretion. This suggests that changes in steroid loss may be the result of changes in glomerular filtration rate; and since increased steroid loss is associated with increased rather than decreased sodium loss, it is believed that the nocturnal steroid diuresis is a secondary rather than a primary phenomenon.

INHIBITOR OF DESOXYRIBONUCLEASE IN CERTAIN MAMMALIAN TISSUES AND ITS RELATIONSHIP TO CELLULAR MATURITY. *H. H. Henstell,* Robert I. Freedman and Ben Ginsburg*, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif.

By means of a viscosimetric technic an inhibitor of desoxyribonuclease was demonstrated

in aqueous extracts of normal human white blood cells and bone marrow cells and in extracts of blood and marrow cells from patients with leukemia or lymphosarcoma. The presence of the inhibitor in cell extracts from rat, mouse and human liver and spleen and from various human and animal cancers was confirmed.

It was shown that normal white blood cells had the largest amount of inhibitory activity, namely 37.4 per cent. Blast cells from acute leukemia had little or no inhibitor. Cells of the normal marrow and of chronic leukemic blood and marrow, which were of intermediate degrees of maturity, had intermediate amounts of inhibitor. Tissue cells, such as liver and spleen, were also found to have relatively large amounts of inhibitory activity as compared to that of various types of malignant cells. The inhibitory activity of tissue cell extracts deteriorated rapidly, whereas that of blood and marrow extracts was reasonably stable. This difference was due to a protective effect of blood plasma on the inhibitor. Plasma was used in some experiments to stabilize the tissue cell inhibitor.

In general, it was noted that the degree of inhibitory activity was related to the stage of cellular maturity. It is postulated that this inhibitor of desoxyribonuclease may control the rate of desoxyribonucleic acid metabolism by regulating the rate of its depolymerization. On the assumption that the desoxyribonucleic acid plays an important part in the processes of cell division and maturation, it is speculated that the inhibitor occupies a key position in the control of cell division and/or maturation.

OXYPOLYGELATIN—A PLASMA VOLUME EXPANDER. *A. R. Higgins, H. A. Harper, J. R. Kimmel, T. W. Burns, R. E. Jones, T. W. D. Smith and C. L. Klein (introduced by Morris E. Dailey)*, Metabolic Research Facility, United States Naval Hospital, Oakland, Calif.

In the search for a substance which possesses suitable clinical and chemical characteristics for use in place of whole blood and plasma for the treatment of oligemic shock in mass casualties, many macromolecular materials have been proposed. This report presents data on the clinical administration of a new proposed plasma volume expander, oxypolygelatin, a modified gelatin.

Fifty units of 5 per cent OPG were administered to forty-two patients. In six of seven patients in oligemic shock clinical improvement and increase in blood pressure resulted. In thirty-five normal subjects the disappearance curve of OPG in the plasma and the urinary excretion curves were studied. The peak level (450 mg. per cent of OPG) in the plasma was reached immediately after infusion and fell off rapidly to 200 mg. per cent in about four hours, when the curve flattened, until at twenty-four hours 60 mg. per cent of OPG remained in the plasma. Detectable amounts of OPG (10 to 30 mg. per cent) were found in the plasma of some patients at forty-eight hours. The urinary excretion of OPG was maximal during the first three hours after infusion, and at eight hours about 50 per cent of the administered OPG had been excreted. Only small amounts were excreted after eight hours. When the total amount of OPG in the plasma was calculated and added to the amount recovered in urine at a particular time after infusion, an increasingly large moiety is unaccounted for, reaching about 50 per cent at eight hours.

Five of forty-five patients receiving OPG showed minor allergic manifestations, with none in recent lots of material. Sedimentation rates increased in all cases. No interference was observed with blood typing or matching. Hematocrit values decreased for a period of approximately two hours in normal subjects.

The data suggest that oxypolygelatin is therapeutically effective and clinically safe in the treatment of oligemic shock.

EFFECT OF AMPHENONE "B" ON ADRENAL AND THYROID. *John R. Hogness and Robert H. Williams,** Department of Medicine, University of Washington, Seattle, Wash.

Amphenone "B," a substituted desoxybenzoin, has been shown by Allen, Hertz and Tullner to produce thyroid and adrenal enlargement as well as progestation in rats. The effects on the thyroid and adrenal can be inhibited by hypophysectomy or by the administration of thyroxine and cortisone, respectively. We have conducted studies to explain more fully the alterations in thyroid and adrenal size and function produced by amphenone "B."

The adrenal enlargement in rats was found to be associated with a 200 per cent increase in adrenal cholesterol concentration. At the same time the adrenals secreted sufficient steroid to produce a marked fall in circulating eosinophils. It is believed that amphenone "B" may exert its adrenomegalic effect by immediate stimulation of the adenophypophysis to produce ACTH

rather than indirectly, as seen for example, in thiouracil-induced goiter.

In addition to thyroid enlargement a marked decrease in I^{131} concentration in the gland was observed after administration of amphenone "B." Radioiodine concentrations were found to be approximately 10 per cent of the control values. Further *in vivo* and *in vitro* experiments have shown that this is most probably due to a thiouracil-type of action. However, the effects noted within the time relationships of our experiments were similar to those produced by TSH and some evidence was obtained favoring an increased rate of secretion of radioiodine as well as a decreased uptake.

PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION. *Herbert Hultgren,* Arthur Selzer,* Ann Purdy and Emile Holman*, Departments of Medicine, Pediatrics and Surgery, Stanford University School of Medicine, San Francisco, Calif.

The usual isolated patent ductus arteriosus is accompanied by a normal or only moderately elevated pulmonary artery pressure in the presence of a frequently large total pulmonary blood flow. This absence of pulmonary hypertension is due to the existence of a normal pulmonary vascular bed which can tolerate large flows without an increase in pressure. Atypical cases, however, have been described in which the pulmonary artery pressure may approach or equal the aortic pressure in the presence of only a small volume of flow through the ductus, or an actual reversal of flow producing arterial unsaturation in the lower extremities. In these instances the pulmonary vascular resistance is greatly elevated. The cause of this elevation is not known but it does not appear to be related to a long-continued elevated pulmonary blood flow. The clinical picture in such cases may be entirely different from that of the usual patent ductus. The value of surgical correction in some cases may be questioned. For these reasons six cases of isolated patency of the ductus arteriosus with marked pulmonary hypertension will be presented and the clinical findings and circulatory physiology discussed. Three patients had cyanosis and polycythemia. In one of these cases the diagnosis was confirmed by autopsy, and in two others cardiac catheterization and arterial oxygen studies were done. Two of three other patients without cyanosis were studied by similar methods. The diagnosis was confirmed by autopsy in two and by surgical division of the ductus in the other.

QUANTITATIVE ASPECTS OF ANTIBIOTIC SYNERGISM AND ANTAGONISM. *Ernest Jawetz* and Janet B. Gunnison*, Divisions of Microbiology, Medicine and Pediatrics, University of California School of Medicine, San Francisco, Calif.

Antibiotic synergism and antagonism have been demonstrated *in vitro*, in infections of experimental animals and in certain human infectious diseases. Fixed "synergistic" or "antagonistic" drug pairs do not exist. Combined antibiotic action is a function of the microorganism's behavior toward the single antimicrobial agents making up the pair. Study of many bacteria isolated from human disease indicates that a given drug pair may be synergistic against one organism, antagonistic when acting on another. A given drug combination exhibits, however, only one type of action against a given microorganism. Synergism is not changed to antagonism, nor vice versa, by altering the concentration or the proportions of members of the drug pair. Although antagonism is always a unilateral interference effect, synergism is a mutual phenomenon. Examples illustrating these generalizations will be presented. An over-all scheme of combined antibiotic action has been formulated:

Antibiotics fall into two distinct groups: (1) penicillin, streptomycin, bacitracin, neomycin; (2) aureomycin, chloramphenicol, terramycin.

Drugs of group 1 are often synergistic with each other, occasionally indifferent, never antagonistic. Drugs of group 2 are never synergistic with, or antagonistic to each other, but frequently additive. Group 2 drugs frequently antagonize group 1 agents acting on group 1-susceptible organisms. On the other hand, group 2 drugs may be synergistic with group 1 when acting on group 1-resistant bacteria. Available experimental and clinical data are in agreement with this scheme which is also supported by studies on bacterial mutants of defined drug susceptibility.

METHOD FOR THE MEASUREMENT OF HEMOGLOBIN SYNTHESIS *In Vitro*. *Wallace N. Jensen, G. E. Cartwright* and M. M. Wintrobe,** Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

By estimating the rate of incorporation of radioactive iron into avian hemoglobin an *in vitro* method has been devised for quantitatively measuring the rate of hemoglobin synthesis.

This method affords a simple means for the study of the nucleated red cell as a metabolic unit in the absence of the multiple influences of various *in vivo* processes.

Duck blood is incubated with Fe^{59} for twenty-four hours at 37°C. The cells are then separated by centrifugation and hemolyzed. The hemoglobin obtained is converted to hemin, purified, recrystallized and dried. It is then weighed and assayed for Fe^{59} content. From the data obtained, the percentage of Fe^{59} utilized in the synthesis of new hemoglobin is calculated.

The data presented concern the standardization of the method and the influence of several factors on the rate of hemoglobin synthesis.

The method is reproducible with a mean variation of 5 per cent ± 0.38. Approximately 40 per cent of the radioiron is incorporated into hemoglobin in six hours, 60 per cent in twelve hours and 90 per cent in twenty-four hours. Iron is accepted into the red cell in a non-hemoglobin state prior to incorporation into hemoglobin. Hemoglobin synthesis takes place more rapidly when cells are incubated in plasma than in saline. The rate of hemoglobin synthesis of cells suspended in saline is accelerated by the addition of either glycine or glucose. The addition of a small amount of KCN completely inhibits the synthesis.

METABOLIC STUDIES OF PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA. EFFECTS OF PROLONGED ADMINISTRATION OF CORTISONE. *Vincent C. Kelley,* Robert S. Ely, Richard B. Raile and Don H. Nelson*, Departments of Pediatrics and Biochemistry, University of Utah, Salt Lake City, Utah.

Wilkins' recent demonstration of the efficacy of cortisone in the therapy of congenital adrenal hyperplasia has given impetus to studies of the metabolic aberrations which exist in patients with this condition. He has demonstated dramatic clinical response and response of certain urinary excretory products, most notably the 17-ketosteroids, to such therapy. Although previous attention appears to have been focused primarily upon these considerations of the problem, certain other metabolic aspects of these patients appear worthy of investigation.

This report is concerned with a variety of metabolic studies performed in our laboratory on four patients with congenital adrenal hyperplasia—two typical female pseudohermaphrodites, one ovariectomized female pseudohermaphrodite and one macrogenitosomia precox. The studies performed include determinations of blood levels of 17-hydroxycorticosteroids and urinary excretion of 17-ketosteroids; of pituitary adrenal response; of electrolytes in the blood; of acute phase substances in the blood; of certain phases of carbohydrate metabolism; and evaluation of clinical and developmental status and response of the patients.

The observations made in the present study concerning the clinical and urinary 17-ketosteroid response to cortisone therapy are in agreement with those previously reported by Wilkins and others. In addition, certain metabolic abnormalities not previously reported in this condition and the effect of cortisone therapy upon them were observed. The data presented here lend additional support to the rationale for the use of cortisone in prolonged therapy of patients with congenital adrenal hyperplasia.

ACCELERATION OF NEOGLUCOGENESIS FROM FAT IN RESPONSE TO ACTH AND CORTISONE IN HUMAN SUBJECTS. *Laurance W. Kinsell,* George D. Michaels, Sheldon Margen, Lenore Boling and John W. Partridge, with technical assistance of Nancy Dawson, George Fukayama, Rosalie Greer and Sadie Smyrl*, Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, Calif.

Previous studies in this laboratory have shown that ACTH and cortisone (1) diminish or eliminate fasting-induced hyperketonemia and (2) increase the rate of disappearance of infused fatty acid without increasing the formation of ketones. From these and other data it has seemed probable that cortisone-like adrenal steroids increase the rate of utilization of fatty acid through other than ketone channels. The present experimental work was designed to determine the presence or absence of acceleration of neoglucogenesis from fatty acids by ACTH and cortisone.

To date, studies have been carried out in three diabetic subjects. During the period of study all patients have been maintained on chemically constant formula intake throughout the twenty-four hours. The formulas have contained no carbohydrate; large amounts of fat; and different amounts of protein in each of the three subjects. After a suitable control period all patients have received ACTH and/or cortisone.

The following results have been obtained: (1) Major increase in glycosuria and urinary nitrogen occurred in all instances during ACTH

and cortisone administration. (2) The proportional increase in urinary sugar was significantly greater than the increase in urinary nitrogen. In numerous instances during the course of each of the three studies the D/N ratio greatly exceeded 3.65. At times the ratio actually exceeded 6.25. (3) In two of the patients major insulin resistance resulted from the administration of ACTH and cortisone. In the third patient (in whom the experimental procedures were modified) no insulin resistance occurred despite progressive hyperglycemia and glycosuria.

One may conclude that cortisone-like steroids resulting from adrenocortical stimulation accelerate the formation of carbohydrate from fatty acid. Observations upon the possible mechanism of steroid hormone-induced insulin resistance will be discussed as time permits.

UTILIZATION OF S^{35}-CYSTINE IN RATS FED PROTEIN DEFICIENT DIETS. *Norman D. Lee and Robert H. Williams,** Department of Medicine, University of Washington School of Medicine, Seattle, Wash.

Female Sprague-Dawley rats, weighing approximately 165 gm., were placed on various artificial diets for seven days and were allowed to feed *ad libitum*. The dietary variation was concerned with the quantity and biologic value of the protein constituent and with non-protein diets supplemented with non-radioactive L-cystine. On the eighth day a standard dose of S^{35}-labeled DL-cystine was administered intraperitoneally and the animals were sacrificed eight hours later. The extent of incorporation of the label into liver and plasma protein was then determined.

It was found that increasing the dietary content of protein-bound cystine resulted in a decrease in the incorporation of isotopic cystine. When the non-protein diet was supplemented with L-cystine, the incorporation of the isotopic amino acid was increased. Furthermore, if nutritionally incomplete proteins such as zein and gelatin were the sole source of dietary protein, the incorporation of isotopic cystine was increased in comparison to similar diets containing complete proteins.

The data were analyzed with respect to the effect of protein depletion and surfeit on the control of the rate of protein synthesis in the liver. Evidence is presented consistent with the hypothesis that the rat adapts to protein depletion by increasing its rate of protein anabolism.

OCCLUSION OF THE THORACIC AORTA FOR LONG PERIODS BY MEANS OF A MECHANICAL SHUNT. *Sanford E. Leeds** *and Morris Culiner*, Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, Calif.

Prolonged occlusion of the normal thoracic aorta in dogs is followed by severe damage to vital structures and death. In order to avoid the deleterious effects of the occlusion the clamped portion of the aorta was by-passed using a roller-type pump with a carotid-femoral artery shunt. By this means a controlled flow of blood from an artery proximal to the occlusion can be shunted to an artery distal to the occlusion thus supplying the spinal cord and viscera with oxygenated blood in adequate amounts.

In the experimental animals it was found that if a plastic tube was inserted through the femoral artery into the thoracic aorta below the occlusion the mortality was reduced remarkably compared to the use of a metal cannula in the femoral artery. Division and suture of the aorta were carried out while occluding the aorta in some animals. This required reversal of the action of the heparin which is required during the mechanical shunting of the blood.

STUDIES IN SULFUR METABOLISM. VII. THE PROTEIN METABOLIC ABNORMALITY OF THE NEPHROTIC SYNDROME AS STUDIED WITH S^{35}-LABELED METHIONINE. *Sheldon Margen, Judith Lange, Harold Tarver, Roy DeLaney and Laurance Kinsell,** Institute for Metabolic Research, Highland Alameda County Hospital, Oakland, and the Department of Biochemistry, University of California, Berkeley, Calif.

A male patient age eighteen years with severe nephrotic syndrome was studied as follows: (1) Following intravenous administration of a tracer dose of S^{35}-labeled methionine, incorporation of the isotope into plasma protein and the urinary excretion of the isotope were determined. (2) Following the administration of sufficient serum albumin to bring the serum level to approximately 3 gm. per 100 cc. (from a pretreatment level of 0.92 gm. per 100 cc.), a second S^{35} study was carried out. (3) The study was continued during ACTH therapy, which in this patient induced complete remission.

One may conclude the following in the nephrotic patient: (1) The rates of both albumin and globulin synthesis are greatly increased as compared to the normal. (2) The rate of synthesis of albumin and the rate of urinary loss of albumin are almost identical. This is true with

or without albumin infusion. (3) The S^{35} content of the urinary protein is identical with that of the serum albumin. (4) ACTH caused rapid cessation of albuminuria and a return to normal of plasma protein levels.

Similar studies in a patient with severe albuminuria and hypoproteinemia in association with diabetic atherosclerosis will also be presented as time permits.

EFFECT OF TESTOSTERONE ON THE HUMAN TESTIS. FURTHER OBSERVATIONS. *Glenn E. Mortimore, C. Alvin Paulsen and Carl G. Heller,** Department of Medicine, University of Oregon Medical School, Portland, Ore.

The morphology and function of the normal human testis is severely altered when testosterone propionate is administered in ordinary clinical amounts, considered to be greater than the average normal daily output. A study of the immediate effects of such treatment reveals: (1) Urinary gonadotrophin excretion is depressed to, or nearly to, zero; (2) the seminal sperm count is reduced to, or nearly to, zero; and (3) testicular morphology is markedly damaged as attested by a striking decrease in tubule size and increase in sclerosis and hyalinization of the peritubular membranes, arrested spermatogenesis, sloughing, necrosis and decrease in number of germ cells, and a decrease and atrophy of Leydig cells.

Testicular biopsies obtained at intervals from five to thirty-one months after stopping treatment (testosterone propionate, 25 mg. daily, twenty-four to ninety-nine days) showed a remarkable recovery from the damaged state noted just prior to stopping treatment. In most instances when biopsies were obtained seventeen months or more after treatment the testis was structurally better than that demonstrated in the initial biopsy. This difference was most striking in testes initially judged poorer than normal.

After stopping treatment urinary gonadotrophin excretion rapidly returns to pretreatment levels. Seminal fluid sperm concentration increases slowly and generally returns to pretreatment levels within one year.

RELATION OF THE HEMATOLOGIC EFFECTS AND BLOOD 17-HYDROXYCORTICOSTEROID LEVELS AFTER ADMINISTRATION OF ADRENAL STEROIDS AND ACTH. *J. G. Palmer, D. H. Nelson, A. A. Sandberg and F. H. Tyler,** Departments of Medicine and Biochemistry, University of Utah College of Medicine, Salt Lake City, Utah.

Single doses of ACTH (65 mg.), cortisone acetate (200 mg.) and compound F acetate (200 mg.) have been administered to normal subjects and the resulting hematologic changes have been correlated with blood levels of 17-hydroxycorticosteroids. Steroid levels rose from an average of 11 μg. to 24 μg. per 100 ml. of plasma following the administration of ACTH intramuscularly, 25 μg. following administration of cortisone orally and 102 μg. following administration of compound F orally. The peak values were reached one hour after cortisone and compound F administration, and one to two hours after ACTH. Thereafter the levels declined to within the normal range in eight hours. The hematologic effects following administration of any one of the three substances included absolute neutrophilia, lymphopenia and eosinopenia, with no significant changes in volume of packed red cells or platelet counts. Neutrophils rose from an average of 5,100 to 14,500 per cu. mm. following the administration of compound F orally, from 4,600 to 9,000 following ACTH and from 4,700 to 8,100 following cortisone orally. Lymphocytes fell from 2,900 to 1,600 per cu. mm. following compound F; from 2,700 to 1,700 following ACTH and from 2,900 to 1,500 following cortisone. Eosinophils fell from 227 to 8 per cu. mm. following compound F, from 241 to 47 following ACTH and from 344 to 25 following cortisone. Maximum changes in all leukocytes occurred at four to eight hours following administration of the hormones or three to six hours following the attainment of maximum steroid levels. No significant alterations in blood 17-hydroxycorticosteroids or in leukocytes were observed during the twenty-four-hour period following the administration of compound F acetate intramuscularly.

INFECTION AND REINFECTION BY HEMOLYTIC STREPTOCOCCI IN EARLY CHILDHOOD. *Lowell A. Rantz,* Margaret Maroney and Joseph M. Di Caprio*, Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

A continuing study of hemolytic streptococcal infection in early childhood has been carried out during the past four years. One phase involved the serial observation of a large group of infants from birth. New infections occurred regularly among the previously uninfected at a rate of approximately 25 per 100 per annum, and reinfections at a rate approaching 50 per 100 per annum throughout the study period.

Seventy-eight additional children were followed up for six months to three years after a recognized hemolytic streptococcal infection. The mean period of observation was 15.7 months. Reinfection was common in this group and occurred at a mean rate of 0.5 per patient per annum regardless of age when first seen.

Detailed serial clinical observations were obtained from thirty-five or more days after 126 group A hemolytic streptococcal infections in 103 different children. Sixty-four occurred in children less than forty-eight months of age. Neither rheumatic fever nor any less well defined manifestations of a non-suppurative poststreptococcal complication was discovered in any of these. Sixty-two were more than forty-eight months of age. Rheumatic fever developed in two and in four others clinical disorders and laboratory abnormalities developed indicating that a similar process in a less well defined form was present. The possible role of reinfection in the pathogenesis of this changing incidence of complications will be discussed.

STUDIES ON THE MECHANISM OF THE ALTERED CHOLESTEROL METABOLISM IN HYPER- AND HYPOTHYROID STATES. *Ray H. Rosenman, Sanford O. Byers* and Meyer Friedman,** Mount Zion Hospital, Harold Brunn Institute for Cardiovascular Research, San Francisco, Calif.

Despite the low plasma cholesterol concentration observed in hyperthyroidism, this state has been found by us to be characterized by a marked increase in rate of cholesterol synthesis. Thus when rats were made hyperthyroid by administration of thyroid extract, a prompt and marked increase in the rate of synthesis of cholesterol was observed, together with an associated increased excretion of the steroid both in the bile and the stool. Exactly opposite findings were obtained in rats made hypothyroid by administration of thiouracil.

The rate of synthesis was measured by two different methods, namely, (1) assay of biliary cholesterol concentration and (2) determination of the rate of incorporation of the radioactive substance, tritium, into body cholesterol. The rate of excretion was determined by independent assay of biliary and fecal contents of sterols.

The mechanism associated with and possibly responsible for these changes in cholesterol metabolism appears to be one intimately involved in the formation and destruction or excretion of cholic acid.

COBALT AND CORTISONE THERAPY OF CHRONIC ERYTHROCYTIC HYPOPLASIA. *Arthur J. Seaman,** Department of Medicine, Division of Experimental Medicine, University of Oregon Medical School, Portland, Ore.

Chronic erythrocytic hypoplasia in both congenital and acquired forms differs from hypoplastic anemia in (1) the presence of a marrow normally cellular except in nucleated erythrocytes and (2) the absence of thrombocytopenia and granulocytopenia. Barring recovery, prognosis is limited by the complications of blood transfusion therapy. Cases presented here indicate that either cobalt or cortisone may induce erythropoiesis in this disease.

The acquired form developed in one sixty-seven year old man after repeated infections and sulfonamide sensitivity reactions. His course is presented as an example of the untreated patient. He required 30.5 L. of blood in sixty-three transfusions prior to his death from a transfusion reaction. Extensive hemosiderosis was demonstrated at necropsy.

One woman, aged forty (acquired form), received 79 L. of blood in 158 transfusions over a sixty-one-month period. After sixty-four days on oral cobalt chloride, 100 mg. daily, active erythropoiesis developed and has persisted for nine months notwithstanding eleven 350-cc. venesections.

A three and one-half month old girl (congenital form) required 60 L. blood in 140 transfusions over the following ten years. After 164 days on oral cobalt chloride (25 mg. daily) active erythropoiesis occurred. Reticulocytosis disappeared when cobalt was discontinued but reappeared on cortisone therapy.

A three month old girl (congenital form) received 6.5 L. of blood as forty-six transfusions over the following twenty-nine-month period. Cobalt therapy failed but cortisone produced active erythropoiesis.

Another girl (congenital form) thirteen months old has required transfusions every three weeks since three months of age. There has been no response to cortisone. Cobalt has not yet been tried.

POTENTIATION OF MORPHINE AND L-ISOMETHADONE ANALGESIA BY DIHYDROGENATED ERGOT ALKALOIDS. *Herbert J. Semler and Norman A. David,** Department of Pharmacology, University of Oregon Medical School, Portland, Ore.

Observations in our laboratory have shown that small doses of dihydrogenated ergot alka-

loids block morphine hyperglycemia in rabbits caused by single doses of 15 mg./kg. morphine sulfate and 5 mg./kg. L-isomethadone, dl-methadone or L-methadone. Based on this we undertook to study the effects of previous administration of ergot alkaloids on analgesic activity produced by morphine and the newer synthetic analgesics. Analgesic action was determined in normal rats using the D'amour-Smith technic. When a dose of 0.03 mg./kg. of CCK No. 179 (hydergine®) was injected subcutaneously thirty minutes before intraperitoneal injection of 6.00 mg./kg. morphine sulfate, the mean percentage increase in reaction time was 161.9 per cent compared to 86.9 per cent for 6.00 mg./kg. of morphine alone. With CCK No. 179 (0.03 mg./kg.) followed by L-isomethadone (4.00 mg./kg.) the mean percentage increase was 138.1 per cent compared to 67.4 per cent for 4.00 mg./kg. L-isomethadone alone. With minimal doses of the analgesics CCK No. 179 (0.03 mg./kg.) followed by 2.00 mg./kg. of L-isomethadone gave a mean percentage increase in reaction time of 119.8 per cent compared to only 13.0 per cent when L-isomethadone was used alone in a dose of 2.0 mg./kg. With DHO No. 180 in a dose of 0.05 mg./kg. plus L-isomethadone (4.00 mg./kg.) an increase of 158.0 per cent was found compared to the 67.8 per cent increase for L-isomethadone alone. Other combinations of the opiates and dihydrogenated ergot alkaloids showed that the potentiation of analgesia was more pronounced when doses of 0.03 to 0.10 mg./kg. of CCK No. 179 or DHO No. 180 were used. Analysis of variance of the data showed this effect to be statistically significant. Administered alone, the dihydrogenated ergot alkaloids showed no significant analgesic action.

In the hospitalized patients who receive analgesics repeatedly for control of severe pain we have found that administration of a single daily injection of 0.3 mg. (1.0 cc.) of hydergine permits a reduction in both the dose and the frequency of administration of the opiate.

CLINICAL EXPERIENCES WITH THYROTROPHIC HORMONE. *Benjamin Simkin and Paul Starr,** Department of Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

Our observations indicate that the administration of thyrotrophic hormone (TSH) to patients is useful in the following clinical situations: (1) differentiation of primary from secondary (pituitary) myxedema; (2) evaluation of the presumed hypothyroid patient who is on thyroid extract therapy; (3) therapy of metastatic cancer of the thyroid gland.

Thyroid radioactive iodine (I^{131}) uptake was found to be the most sensitive indicator of stimulation of the thyroid gland by TSH. The administration of TSH to euthyroid patients or patients with panhypopituitarism results in an increase of thyroid I^{131} uptake. The thyroid I^{131} uptake is not increased by TSH injections in patients with primary myxedema. Similar results were obtained in patients receiving thyroid extract therapy which did not have to be discontinued in order to establish the diagnosis of these patients.

In patients with metastatic cancer of the thyroid gland administration of TSH was found to increase the radioiodine pickup of metastatic lesions thus allowing these patients to become suitable candidates for I^{131} therapy. Administration of TSH was also found to be useful for the detection of metastatic foci of thyroid malignancy.

None of the twenty-one patients receiving injections of TSH developed exophthalmos as determined by careful serial measurements with the Hertel exophthalmometer. The duration of the TSH injections varied from three days to two weeks, and the doses of TSH were physiologically adequate as seen in the clinical results already given.

BIOCHEMICAL STUDIES ON LEUKOCYTES IN THE MYELOPROLIFERATIVE SYNDROMES. *William N. Valentine,** *William S. Beck, James H. Follette and Harold Mills,* Los Angeles, Calif.

Studies are reported on the biochemical patterns of glycogen, histamine and phosphatase activity in separated leukocytes from subjects with various myeloproliferative syndromes. Two distinctive patterns of rather remarkable uniformity are apparent.

First, the pattern exhibited in typical chronic myeloid leukemia is characterized by high unit cell and total blood histamine, markedly low unit myeloid cell alkaline phosphatase and (on the basis of preliminary data) low unit myeloid cell glycogen.

Second, the pattern of typical polycythemia vera in patients with leukocytosis and/or differential formula alterations is characterized by a similar but less dramatic aberration in blood histamine, markedly elevated alkaline phosphatase activity and high glycogen content per

unit myeloid cell. The second pattern persists in subjects who late in their illness develop marked splenomegaly, anemia, a peripheral blood picture difficult to differentiate from that of chronic myeloid leukemia, and/or the clinical suspicion of myelofibrosis. Myelofibrosis has also been observed in an elderly patient with the complete metabolic aberrations of the first pattern and does not appear specific to either pattern. A single case of agnogenic myeloid metaplasia conformed to the second pattern. This pattern has not been observed in secondary polycythemia to date. Both patterns are substantially different from those thus far observed in the more readily differentiated leukocytoses of other etiology and leukemoid "irritative" reactions associated with marrow metastases. Neither is explainable by variations in differential formulas.

ALTERATION OF THE ACTION OF INSULIN ON GLUCOSE METABOLISM BY BETA-HYDROXYBUTYRIC ACID. *Arne N. Wick* and Douglas R. Drury,** Scripps Metabolic Clinic, La Jolla, Calif., University of Southern California, Los Angeles, Calif.

Ketone bodies can be an important source of energy for the tissues. Their utilization can be increased by raising their concentration in the circulating fluids. Thus 50 per cent or more of the total oxygen consumption of the tissues can be through ketone body oxidation.

With isotope technic it has been definitely established that oxidation of glucose by the tissues can be increased two- to threefold by insulin. We have then two methods of experimentally changing the type of fuel used by the tissues, and by the simultaneous application of both of these information should be obtained that might give some insight into the ways these substances are utilized by the body cells.

Eviscerated rabbits were given maximal dosages of insulin and just enough C^{14}-labeled glucose to maintain the blood sugar at a normal level for eight hours. The CO_2 was collected for radioactivity determination. For the first five hours insulin and glucose were given, and then for three hours in addition to these beta-hydroxybutyric acid was given. In this way the effect of the beta-hydroxybutyric acid on the glucose oxidation and requirement could be determined.

The addition of beta-hydroxybutyric acid had little effect on the glucose requirement. There was a marked decrease in the amount of glucose oxidized. These results indicate that beta-hydroxybutyric acid does not affect the action of insulin in transferring glucose into the cells but does compete with glucose for terminal oxidation within the cell.

CARDIOVASCULAR AND RENAL ADJUSTMENTS TO A NEW HYPOTENSIVE AGENT (CIBA-5968). *Ernest L. Wilkinson, Heikki Backman and Hans H. Hecht,** Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

1-Hydrazinophthalazine (Ciba-5968) has been demonstrated to increase renal blood flow (Reubi, 1950) and to lower arterial pressures in man (Schroeder, 1951). This unique combination of effects has not been reported hitherto for other chemical compounds proposed as antihypertensive agents. We have therefore investigated the effects of a single intravenous dose (0.25–0.50 mg./kg.) on renal function, arterial pressure and cardiac output.

A moderate increase in renal plasma flow (C_{PAH}) was regularly present with an average maximum rise of 38 per cent (11–122 per cent). No consistent change in glomerular filtration rate (C_I) occurred but the filtration fraction fell regularly. A significant diuretic action was a frequent but inconstant effect. Within a few minutes following the administration of the compound the heart rate increased by about 50 per cent. Cardiac output and stroke volume measured in four subjects by cardiac catheterization rose sharply with an average maximum increase of 112 per cent within fifteen to forty-five minutes. Pulmonary artery pressures increased slightly. The average fall in total systemic peripheral resistance in these subjects was 61 per cent. The systemic diastolic blood pressure decreased in eight normals by an average of 18 mm. Hg within twenty-two minutes; the fall in six hypertensive subjects measured 35 mm. Hg and only infrequently returned to the predrug level within two hours. Changes in systolic pressure were less striking.

This compound causes sustained increase in cardiac output and stroke volume with a fall in arterial pressure. It increased renal plasma flow but this was less than expected from the increase in cardiac output. Its therapeutic possibilities are obvious although at present frequent minor toxic effects and the inconstant oral action of the drug have limited its usefulness in ambulatory patients.

METABOLISM OF RADIOACTIVE ACETATE BY HUMAN TUBERCLE BACILLI. *Richard J. Winzler,* Cornelius Y. Chiamori and Hisako Nishahara,* Department of Biochemistry and Nutrition, University of Southern California, Los Angeles, Calif.

Experiments have been initiated which are designed to elucidate some biosynthetic processes of mycobacteria and the mechanism by which bacteriostatic agents inhibit the growth of mycobacteria. A virulent strain (H37Rv) and a streptomycin-resistant strain (H37RvSR) of human tubercle bacilli have been cultured in 200 ml. of Proskauer-Beck medium for fourteen days. One-tenth milligram of acetate-1-C^{14} containing one microcurie of C^{14} was added, and the incubation continued for one week. The bacteria were harvested by filtration, and the radioactive carbon in the carbon dioxide, the saponifiable and non-saponifiable lipids and the protein fractions was determined. The streptomycin-resistant strain oxidized a greater proportion of the acetate to carbon dioxide and incorporated more radioactivity into the lipids and proteins than did the sensitive strain. The presence of streptomycin at a concentration of 100 mg./L. completely inhibited growth of the sensitive strain but had no significant influence on the incorporation of radioactive carbon from acetate into the saponifiable and non-saponifiable lipids, and only a slight inhibitory effect on the incorporation into the protein fraction of either the sensitive or resistant strains. This indicated that protein and lipid turnover can occur independently of growth and that the inhibitory effects of streptomycin on the sensitive strain are not mediated through interference of the turnover of these gross cell fractions. Further studies on the specific activities of individual amino acids, nucleotides and certain of the characteristic lipids such as mycolic acid and phthioic acid are being carried out in an effort to localize the site of action of streptomycin.

REDUCED RENAL EXCRETION OF SODIUM CHLORIDE FOLLOWING CIRCULATORY STRESSES. *W. B. Youmans,* D. M. Bachman and P. H. Blachly,* Department of Physiology, University of Oregon Medical School, Portland, Ore.

The effects of each of the following procedures on glomerular filtration rate (GFR) and renal excretion of NaCl have been studied using dogs: (1) anesthetization by rapid intravenous injection of sodium pentobarbital; (2) rapid withdrawal of blood and subsequent reinjection; (3) vertical position of body after adrenergic blockade with dibenamine; (4) rapid intravenous injection of 1 to 4 mg. of acetylcholine. In two patients with postural hypotension the effects of the orthostatic position on GFR and sodium chloride excretion were determined.

Each of the aforementioned procedures may produce and some of them routinely produce a decrease in GFR. When the GFR is decreased, there is a much greater percentage decrease in or a virtual cessation of NaCl excretion. After termination of the stress rapid recovery of GFR to control levels or above is the rule, while the NaCl excretion does not show a corresponding recovery or remains at the minimum level for a prolonged period.

The rate of excretion of NaCl in the two patients with orthostatic hypotension during a period of several hours when they were up and about was one-fifth to one-twentieth of the rate for the period when they were recumbent. During the first part of the "up" period the minimum GFR and sodium chloride excretion rate were observed; then some recovery of each rate occurred. When the patient was returned to the recumbent position after being up for several hours, the GFR quickly returned to normal levels but sodium chloride excretion was restored quite gradually.

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SOUTHERN SECTIONAL MEETING HELD IN ATLANTA, GEORGIA, JANUARY 18, 1952

EFFECT OF HEXAMETHONIUM (C_6) ON RENAL HEMODYNAMICS. LABORATORY AND CLINICAL EVALUATION. *L. C. Mills, M.D. (by invitation), J. H. Moyer, M.D. and C. A. Handley, Ph.D. (by invitation).* (From the Departments of Medicine and Pharmacology, Baylor University College of Medicine and the Cardiac Clinic, Jefferson Davis Hospital, Houston, Tex.)

Because of its hypotensive effect on patients with essential hypertension, the effect of hexamethonium on renal hemodynamics was studied to determine whether there was an associated alteration in renal function. Glomerular filtration rate, RPF and TmG were determined in seven dogs, GFR, RPF, Na and K excretion, and hematocrit in six hypertensive patients with minimal to moderate renal disease and two normotensive patients. Following the intravenous administration of 2 mg./kg. of hexamethonium chloride to the seven dogs the mean blood pressure was decreased to about 70 per cent of the control value. There was no significant change in GFR, TmG or RPF, except in the dogs in whom the hypotensive effect was most marked. In these the RPF was somewhat depressed. Similar results were obtained on the two normotensive patients studied. Following the intravenous administration of 20 to 40 mg. of hexamethonium chloride to hypertensive humans, the mean blood pressure was decreased to 75 per cent, the GFR to 65 per cent and RPF to 89 per cent of the control values. The hematocrit was slightly decreased and urine flow was markedly depressed.

These observations were interpreted as indicating that, associated with the hypotensive response to hexamethonium, renal vasodilatation takes place in normal kidneys as indicated by a decrease in renal vascular resistance. This results in a maintained RPF and GFR. However, the fact that GFR and RPF were diminished significantly in the hypertensive patients indicates that the diseased kidney is unable to compensate for a moderate depression of blood pressure.

EFFECT OF ACUTE REDUCTION OF ARTERIAL PRESSURE USING HEXAMETHONIUM ON THE MANIFESTATIONS OF CONGESTIVE HEART FAILURE IN MAN. *Robert T. Kelley, M.D. (by invitation), Thomas F. Higgins, M.D. (by invitation) and Edward D. Freis, M.D.* (From the Veterans Administration Hospital, Washington, D. C.)

In the treatment of congestive heart failure the possible value of agents which decrease vascular resistance has not been extensively investigated, despite the observations of Starling that decrease of total peripheral resistance improves the output of the isolated dog's heart.

The immediate effects of hypotensive doses of intravenous hexamethonium was determined in acute experiments in ten patients with congestive failure. In all cases the venous pressure was reduced by 18 to 132 mm. water (mean 77 mm.). The arm to tongue circulation time decreased significantly in seven instances (range 26 to 54 per cent, mean 41 per cent). In seven patients the heart rate decreased from 5 to 19 beats per minute (mean 12). Three of five cases exhibiting orthopnea showed definite improvement in this symptom. Increase in vital capacity occurred in three of eight patients tested. These evidences of improvement were observed in normotensive as well as hypertensive types of heart disease. Electrocardiographic changes consisted of prolongation of the Q-T interval in eight of nine cases studied and slightly greater inversion of T waves in four patients. These studies suggest that decrease of peripheral resistance may benefit cardiac failure in man as in the experimental animals.

STUDIES IN VASOSPASM. AN EVALUATION OF WEAK OR ABSENT PERIPHERAL PULSES. *William T. Foley, M.D., Ellen McDevitt, M.D. (by invitation), John Tulloch, M.D. (by invitation), Martin Tunis, M.D. and Irving S. Wright, M.D.* (From the Vascular Section, Department of Medicine, Cornell University Medical College, New York, N. Y.)

A group of one hundred individuals with various peripheral vascular diseases, increased

and normal vasomotor tone, were studied. Observations were made on the character and quality of the pulses of the wrists and feet, oscillometric readings, blood pressure, pulse rate and clinical evaluation of vasomotor tone of hands and feet as denoted by color, warmth and moisture following the administration of various vasodilating agents. In a selected group of thirty patients skin temperature studies and arterial pulse tracings were made in addition by means of electronic equipment in a constant temperature room.

Absent or weak pulses due to vasospasm can be increased to full bounding pulses in a period of less than three minutes by the sublingual administration of nitroglycerine. Organically blocked or narrowed arteries give an increase equal only to the degree of spasm present. This observation serves to provide a simple, quick bedside test to distinguish the absent pulse due to vasospasm from that due to organic occlusion.

OBSERVATIONS ON THE NORMAL SPATIAL VECTORCARDIOGRAM. *J. A. Abildskov, M.D., C. E. Jackson, M.D. (by invitation), J. A. Cronvich, M.S. and G. E. Burch, M.D.* (From the Department of Medicine, Tulane University School of Medicine, New Orleans, La.)

Theoretic considerations indicate that spatial vectorcardiograms may provide data not available from conventional electrocardiograms and limited experience seems to confirm this. Before spatial vectorcardiography can be properly applied to abnormal cardiac states, however, it is necessary to have a better knowledge of the normal variations. It was thought, therefore, that certain features of the vectorcardiograms of seventy-five normal young male adults studied to date would be of interest.

The results can be summarized as follows: (1) Although planar projections showed wide variations, as are encountered among normal electrocardiograms, sixty-six of the three-dimensional vectorcardiograms could be described as positional variants of a single basic pattern, indicating the important role of cardiac position in determining the form of the electrocardiogram. (2) Because of the claim that the precordial leads can be derived from the vectorcardiogram, such an analysis was made in sixty-three of the records. In none of these could detailed characteristics be obtained and in ten, the predicted form of the precordial leads was abnormal, whereas the leads actually recorded were normal.

STUDIES ON AN ELECTROCARDIOGRAPHIC MANIFESTATION OF HYPOXEMIA. *Dan C. Roehm, M.D. (by invitation), Ross C. Kory, M.D. and George R. Meneely, M.D.* (From the Research Laboratory and Medical Service, Thayer Veterans Administration Hospital and the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.)

The changes in the duration of the Q-T interval during the course of the Levy hypoxemia test have been analyzed with corrections for heart rate (Bazett). The duration of mechanical systole was estimated by measuring from the peak of the R wave in V_4 to the onset of the second heart sound (A_2) in a simultaneous phonocardiogram. Normal volunteer subjects and a group of patients with coronary artery disease with positive hypoxemia tests were studied. The normal subjects exhibited a mean QTc maximal increase of 0.014 ± 0.010 seconds during the hypoxic period as compared with a mean increase of $0.038 \pm .012$ seconds in the patients. Following oxygen administration the control group showed a mean decrease in QTc of $0.015 \pm .013$ seconds as compared with $0.041 \pm .022$ seconds for the patients. Several additional patients with strong objective evidence of coronary artery disease with negative hypoxemia tests did not differ appreciably from the abnormal group in Q-T response. The changes in $R\text{-}A_2$ closely paralleled the Q-T changes in the normal subjects but not in the patient group. It is suggested that careful Q-T measurements may furnish additional information in evaluation of the hypoxemia test.

TREATMENT OF BARBITURATE POISONING BY HEMODIALYSIS. *W. P. Walsh, M.D. (by invitation), L. H. Kyle, M.D., P. D. Doolan, M.D. and H. J. Jeghers, M.D.* (From the Department of Medicine, Georgetown University Medical Center, Washington, D. C.)

These studies to determine the feasibility of use of the artificial kidney in the treatment of barbiturate poisoning compare the amount of barbiturate removed by hemodialysis with that obtained by normal renal excretion. Two patients with chronic uremia were given a therapeutic dose of barbiturate prior to dialysis. Two normal persons were given a similar dose and urinary excretion was measured. Removal of the drug by hemodialysis was much more efficient. Urinary excretion of the drug was measured in three patients with barbiturate poisoning under varying conditions of hydra-

tion. Urinary excretion varied between 2 and 13 mg. of barbiturate per hour, the higher values being associated with massive hydration. In a control patient with a comparable blood level of barbiturate who underwent dialysis by the artificial kidney the average removal of barbiturate was 121 mg. per hour. One patient with severe barbiturate poisoning excreted 71 mg. of barbiturate in a urine volume of 1,240 cc. over a period of twelve hours just prior to hemodialysis. After a five-hour dialysis 739 mg. of the drug were found in the bath. In terms of hourly excretion 6.0 mg. were removed by the kidneys and 148.0 mg. by hemodialysis. This patient was completely areflexic and unresponsive to analeptic therapy after thirty-six hours of conservative treatment prior to dialysis but following this procedure she responded readily to picrotoxin.

On the basis of these findings it may be concluded that barbiturates are removed at least fifteen to twenty-five times more effectively by hemodialysis than by normal urinary excretion and the use of the artificial kidney is recommended for the treatment of severe barbiturate poisoning.

METHYL ALCOHOL POISONING. EXPERIENCE WITH 320 CASES. *Ivan L. Bennett, Jr., M.D., George L. Mitchell, Jr., M.D. (by invitation), Freeman H. Cary (by invitation), Manuel Cooper (by invitation) and James D. Evans (by invitation).* (From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.)

Observations have been made on 320 patients who ingested bootleg whiskey contaminated by methyl alcohol. By far the most important factor in treatment and prognosis is the degree of acidosis produced by the intoxication. Of 112 patients with lowered plasma bicarbonate, 18 per cent died. Of twenty-seven patients with plasma bicarbonate below 10 mEq., 48 per cent died. Vigorous alkalinization by intravenous infusion of sodium bicarbonate in 3 or 5 per cent solution resulted in prompt alleviation of symptoms in most cases. Exceptions were eight patients who were moribund on arrival and three patients who remained comatose despite restoration of bicarbonate to normal and died after several days. Laboratory data of interest included the finding of higher levels of methyl alcohol in the cerebrospinal fluid than in the blood as well as the detection of methyl alcohol in gastric washings as late as four days after ingestion. Serum Na^+ and K^+ levels were normal even in severely acidotic patients before therapy. After infusion of large amounts of sodium bicarbonate, hypokalemia was occasionally encountered. Acetonuria was common and blood ketone levels were elevated although this elevation was not of a degree sufficient to explain the extreme acidosis. An interesting finding was elevation of serum amylase; pancreatic lesions were noted at autopsy in several patients. Visual disturbances accompanied by characteristic retinal changes were observed in about 50 per cent of acidotic patients.

EFFECTS OF METHYL AND ETHYL ALCOHOL ON CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION. *Louis L. Battey, M.D. (by invitation), John L. Patterson, M.D. (by invitation) and Albert Heyman, M.D.* (From the Departments of Medicine and Physiology, Emory University School of Medicine, and Grady Memorial Hospital, Atlanta, Ga.)

The cerebral blood flow (CBF) and metabolism ($CMRO_2$) were studied by the nitrous oxide method in five patients with methyl alcohol poisoning, four patients with delirium tremens and ten individuals given intravenous infusions of ethyl alcohol. The patients with methanol ingestion were confused or comatose and had a mean CBF of 36 cc. and a $CMRO_2$ of 2.0 cc./100 gm. brain/min., compared with the normal values of 50 cc. and 3.1 cc., respectively. Repeat studies in four of these patients during recovery showed that two of them had a significant increase in both CBF and $CMRO_2$ while two others had no change in these functions. The four patients with delirium tremens also showed a definite reduction of cerebral blood flow and oxygen consumption, with values of 34 cc. and 2.4 cc., respectively. The administration of 85 to 300 cc. of 5 to 10 per cent alcohol intravenously in normal individuals produced drowsiness and euphoria, but no significant change either in blood flow or oxygen consumption.

These studies provide further evidence of the striking difference in the acute toxicity of methanol and ethanol. They also demonstrate the metabolic abnormalities which would be anticipated from the clinical and pathologic findings in delirium tremens. Ethanol in the dosages employed is not an efficient cerebral vasodilator.

EFFECT OF EXPERIMENTAL METABOLIC ALKALOSIS ON CEREBRAL BLOOD FLOW. *J. F. Schieve, M.D.*

and W. P. Wilson, M.D. (by invitation). (From the Departments of Medicine and Psychiatry, Duke University School of Medicine, Durham, N. C.)

Cerebral vascular tone is predominantly under chemical control. Respiratory acidosis produced by carbon dioxide inhalation causes increased cerebral blood flow (CBF) and cerebral vasodilatation. Respiratory alkalosis produced by hyperventilation results in decreased CBF and cerebral vasoconstriction. These studies fail to separate which factor, arterial blood pH or CO_2 content, is more important in regulating cerebral vessel tone.

Using the nitrous oxide method for measuring CBF fifteen patients were studied before and toward the end of rapid intravenous infusions of 3 per cent $NaHCO_3$ (nine patients) and normal saline (six patients). Both fluids were given at the same rate (15 cc. per minute), in equal quantities (900 cc.) and over the same time period (one hour). Neither was accompanied by subjective sensations nor changes in pulse rate, blood pressure or respiratory rate. A similar degree of hemodilution occurred following both types of infusions.

Sodium bicarbonate produced a marked consistent increase in CBF (65 per cent) comparable in magnitude to that following inhalation of 5 per cent CO_2. No change in cerebral oxygen consumption resulted. Arterial blood pH changed from 7.35 to 7.53. Normal saline produced no change in CBF, cerebral oxygen consumption or arterial blood pH. This study suggests that the bicarbonate ion is more important than pH in controlling cerebral vascular tone.

Effects of Intravenous Papaverine and Procaine on Cerebral Blood Flow and Metabolism. *Peritz Scheinberg, M.D., Harold W. Jayne, M.D. (by invitation), Ione Blackburn (by invitation), Maurice Rich, M.D. and Martin S. Belle, M.D.* (From the Department of Experimental Medicine, University of Miami Medical Research Unit, and the Department of Medicine, Veterans Administration Hospital, Coral Gables, Fla.)

Papaverine and procaine have both been used in the treatment of various cerebral vascular and metabolic disorders. Symptoms of procaine toxicity are thought to be due to a deleterious effect of the drug on the brain. The purpose of this study was to measure the effects of intravenous papaverine and procaine on cerebral metabolic functions in man by use of the nitrous oxide technic for cerebral blood flow.

In eighteen patients administration of 200 mg. papaverine in ten minutes resulted in a 13 per cent increase in cerebral blood flow, with no change in cerebral oxygen consumption, a 13 per cent reduction in mean arterial pressure and a 17 per cent reduction in cerebral vascular resistance. These changes were thought to be due to a direct vasodilating action of the drug, which was quantitatively as effective in elderly as in young subjects. In sixteen patients administration of 750 mg. procaine in twenty minutes resulted in no significant effect on cerebral blood flow or oxygen consumption, but did produce a questionably significant increase (14 per cent) in cerebral vascular resistance. None of the patients showed clinical toxicity to the drug. Seventy-five mg. priscoline intravenously produced no apparent change in cerebral blood flow in five patients.

Alveolar Arterial Oxygen Pressure Gradient in Anemia. *J. B. Hickam, M.D. and J. M. Ryan, M.D. (by invitation).* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

It is generally thought that arterial oxygen tension is normal in anemia. The advent of sensitive methods for measuring blood oxygen tension and the finding that breathing is significantly influenced under certain conditions by changes in arterial oxygen tension which are difficult to detect by older methods suggested that the problem be re-investigated in connection with the dyspnea of anemia.

Arterial blood gas tension was measured by the method of Riley and colleagues, and alveolar oxygen tension was calculated by the alveolar equation. Measurements were made on ten anemic patients (mean Hgb. 5.7 gm. per cent) and eleven control subjects (mean Hgb. 12.9 gm. per cent), none of whom had congestive failure or pulmonary disease. The arterial blood oxygen tension was 94.1 ± 2.4 mm. Hg for the normal subjects and 82.1 ± 2.6 for the anemic subjects ($p < .01$). The alveolar-arterial oxygen pressure gradient (A-A gradient) was 4.2 ± 2.0 for the normal and 20.5 ± 4.6 for the anemic group ($p < .01$). On 15 per cent O_2, the A-A gradient of the anemic group fell to 3.3 ± 4.0 mm. Hg. A-A gradient and hemoglobin had a significant negative correlation.

Anemic persons have a distinctly reduced

arterial O_2 tension which becomes lower as the anemia becomes more severe. This is probably a significant factor in the exertional dyspnea of anemia.

ESTIMATION OF THE VOLUME OF THE EXTRACELLULAR FLUID WITH RADIOACTIVE SULFATE. *M. Walser, M.D., D. S. Seldin and C. H. Burnett, M.D.* (From the Department of Internal Medicine, Southwestern Medical School of the University of Texas, Dallas, Tex.)

S-35 labelled sulfate offers several theoretic advantages over many other substances used to measure extracellular fluid volume: no correction for endogenous substance is necessary; renal loss is relatively slow; and, since a negligible weight of sulfate is injected, no change in internal fluid exchanges by osmotic effects is produced. A method for analysis of radioactive sulfate in plasma and urine with an error of about 1 per cent was developed. Analysis of the arterial concentration time curve in normal subjects showed that equilibration after intravenous injection proceeded rapidly at a single exponential rate and was essentially completed in eighteen minutes. The eighteen-minute volume of distribution of radiosulfate, corrected for urinary loss, was 13 to 19 per cent of body weight in ten normal subjects. In a given subject results were usually reproducible within 0.3 L. or less. After equilibration the progressive increase in volume of distribution was slow, suggesting that the eighteen-minute volume of distribution does not include a significant portion of cell water. The determination of extracellular fluid volume by this method offers distinct advantages over most other methods in that it involves only a single injection which equibrates rapidly and is without osmotic effects.

EFFECT OF CORTISONE AND ACTH ON RENAL EXCRETION OF CHLORIDES. *J. E. Kimbrough, B.S. (by invitation), R. M. Lightfoot, B.S. (by invitation) and Howard L. Holley, M.D.* (From the Department of Medicine, Medical College of Alabama, Birmingham, Ala.)

A chloride deficit alkalosis commonly develops in patients treated with corticotropin and cortisone. To determine the mechanism of the production of the chloride loss by way of the kidney studies of urinary chloride excretion together with urinary volume were performed on six patients receiving corticotropin and cortisone. Patients were placed on a fixed diet—identical from day to day—for a control period for not less than forty-eight hours before hormonal therapy was instituted. Twenty-four-hour urine specimens were collected throughout the period of study, including at least one twenty-four-hour specimen prior to initiation of therapy. The urinary chlorides were determined by the Arnold modification of the Volhard technic. Patients treated with cortisone showed a definite increase in total urinary chloride excretion beginning shortly after the onset of therapy and a concomitant increase in urinary volume. However, the minute concentration of chloride per unit of urine before and after therapy did not change. Although the total chloride excreted was increased, there was no selective increase in excretion of this ion. The inhibiting action of cortisone on the antidiuretic hormone no doubt accounted for the diuresis which was accompanied by chloride loss from the body.

Patients receiving corticotropin therapy showed a consistent initial retention of water and chloride followed shortly by a pattern of water and chloride excretion similar to that in patients on cortisone therapy. Early elaboration of the electrolyte retaining hormone, similar to desoxycorticosterone, by the adrenal cortex under influence of the stimulating drug was thought to account for this early pattern of chloride and water retention.

THE REDOX REACTION OF LEUKOCYTES OF NORMAL INDIVIDUALS AND PATIENTS WITH DISSEMINATED LUPUS ERYTHEMATOSUS. *S. N. Chaudhuri, M.D. (by invitation) and Samuel P. Martin, M.D.* (From the Department of Medicine, Duke University School of Medicine, Durham, N. C.)

A quantitative method for the study of human leukocytes with redox dyes has been applied to disseminated lupus erythematosus. A relatively pure suspension of white cells is obtained by dextran sedimentation of the erythrocytes. These cells are incubated with homologous or normal plasma, a dye (2–6 dichlorophenolindophenol $Eh_0 + 0.217$) is added and the rate of conversion to the leuco form is measured by a photoelectric spectrophotometer.

The cells from patients with lupus erythematosus after exposure to buffered saline, normal plasma or plasma from the patient convert the dye slowly and never completely. The cells from normal individuals exposed to buffered saline or normal plasma have a brisk reduction rate but after thirty minutes exposure to plasma from patients with lupus erythematosus lose this characteristic. The factor responsible for this is very labile.

Therapy with ACTH produces a return of the ability of the cell to reduce the dye and the plasma will no longer interfere with normal cells even though it still induces morphologic changes in the cells. This type of dye reaction has been noted in all patients with disseminated lupus studied, an occasional patient with discoid lupus and in rare moribund individuals with other diseases.

BACTERIAL ENDOCARDITIS DUE TO PSEUDOMONAS AERUGINOSA—TREATED WITH NEOMYCIN. *Wilbur L. Kenoyer, Capt., U.S.A.F. (M.C.) (by invitation), Charles T. Stone, M.D. (by invitation) and William C. Levin, M.D.* (From the Department of Internal Medicine, The University of Texas Medical Branch, Galveston, Tex.)

The literature contains reports of eleven cases of bacterial endocarditis due to Pseudomonas aeruginosa with no recoveries. The present report describes a case of bacterial endocarditis caused by this organism in which treatment with neomycin was followed by recovery.

A twenty year old white male had been known to have rheumatic heart disease since the age of seven. Valvular lesions consisted of mitral stenosis and insufficiency and aortic insufficiency. He had a febrile illness of one week's duration when hospitalized. Blood cultures were taken and treatment was instituted with penicillin and streptomycin. There was slight initial improvement but relapse occurred in one week. The blood cultures yielded Pseudomonas aeruginosa which was insensitive to penicillin, aureomycin, chloramphenicol, streptomycin and terramycin at attainable blood levels, but was sensitive to neomycin in a concentration of 5 μg./cc. Neomycin was given intramuscularly in a dosage of 0.5 gm. every six hours. Within thirty-six hours the fever subsided and the patient became asymptomatic. All subsequent blood cultures were negative. Within fourteen days, bilateral high frequency hearing loss was noted and the drug was discontinued. This hearing loss has persisted although there is minimal loss in the spoken voice range. The remission of the bacterial endocarditis has persisted for four months. No appreciable change in the cardiac status has occurred.

This report indicates that neomycin may be used successfully in the treatment of an infection previously considered to be universally fatal. The drug is extremely toxic and its use should be reserved for infections with organisms insensitive to other antibiotics. During therapy with neomycin careful attention should be given to development of toxic reactions.

ABSORPTION, DISTRIBUTION AND EXCRETION OF INTRAMUSCULARLY ADMINISTERED CHLOROMYCETIN IN ACETYL DIMETHYLAMINE AND ORALLY ADMINISTERED CHLOROMYCETIN PALMITATE. *Ellard M. Yow, M.D., H. E. Carnes, M.D. (by invitation), Joseph Hirsch, M.D. (by invitation), R. A. Frankel, M.D. (by invitation) and F. W. Taylor, M.D. (by invitation).* (From the Department of Medicine, Baylor University College of Medicine, Houston, Tex.)

The absorption, distribution and excretion of two new forms of chloromycetin were studied in forty-one patients varying in age from one month to seventy-eight years. Body fluid levels were determined by both microbiologic assay and a colorimetric method based on the reduction of chloromycetin with stannous chloride, diazotization and coupling with the Bratton-Marshall reagent.

Following single intramuscular injections of chloromycetin in acetyl dimethylamine there was a slight initial rise, followed by a gradual fall in the blood level over a period of eight to twelve hours. Although 50 to 60 per cent of the drug was excreted in the urine in twenty-four hours, the blood level curves suggested slow and inconstant absorption. When chloromycetin was given intramuscularly at four-hour intervals, higher blood levels were attained but the levels were not consistent. Cerebrospinal fluid and pleural fluid concentrations of the drug were about half the serum levels.

A tasteless ester of chloromycetin was administered orally to thirty-two patients using varying dosage schedules. Following the administration of single doses peak levels were reached in two hours and detectable levels were present for twelve to twenty-four hours. Relatively constant levels were maintained when the drug was administered every six to eight hours, comparable to those obtained following the oral administration of crystalline chloromycetin. The drug diffused into the cerebro-spinal fluid and pleural fluid, and was largely excreted in the urine in twenty-four hours.

PHOTOMETRIC ANALYSIS OF CERTAIN LIGHT ABSORPTION PROPERTIES OF INTRAEPITHELIAL CARCINOMA, INVASIVE CARCINOMA, SQUAMOUS METAPLASIA AND NORMAL EPITHELIUM OF THE CERVIX UTERI. *Alvan G. Foraker, M.D.* (From the Departments of Pathology of Emory Univer-

sity School of Medicine and Grady Memorial Hospital, Atlanta, Ga.)

Differences in some light absorption properties between normal, metaplastic and neoplastic epithelium were measured photometrically in three groups of twenty patients each with invasive carcinoma, intraepithelial carcinoma and squamous metaplasia of the cervix. Optical densities (D) and "coefficients of basophilia" (B) were determined. These factors are believed to be expressions of cell nucleoprotein content.

The results showed: (1) Equivalent mean optical densities and "coefficients of basophilia" of neoplastic epithelium in invasive (D = 0.400; B = 0.951) and intraepithelial (D = 0.415; B = 0.941), these values being higher than those for metaplastic (D = 0.286; B = 0.888) or normal (D = 0.259; B = 0.908) epithelium; (2) equivalent mean optical densities of normal epithelium regardless of associated lesion. (3) greater computed "basophilia" of normal epithelium associated with invasive (B = 0.918) and intraepithelial (B = 0.920) carcinoma than with squamous metaplasia (B = 0.886).

Carcinoma may stimulate "basophilia" (e.g., nucleoprotein content, etc.) in adjacent normal epithelium, may arise in epithelium with increased nucleoprotein content, and increased nucleoprotein content of squamous epithelium may precede histologically identifiable carcinoma.

The similar light absorption properties of invasive and intraepithelial carcinoma lend support to the concept that these two lesions are only different stages of a neoplastic process.

HISTOCHEMICAL STUDIES OF HUMAN LIVER BIOPSIES. *W. Lane Williams, Ph.D., F. W. Hoffbauer, M.D. and Richard B. Aronsohn, B.A. (by invitation).* (From the Departments of Anatomy and Medicine, and University Hospitals, University of Minnesota, Minneapolis, Minn.)

Decreased ribonucleic acid (RNA) content and positive alkaline phosphatase (APh) activity were observed in parenchymal cytoplasm of livers showing (1) minimal to extensive cirrhosis, (2) carcinomatous metastases, (3) hemosiderosis, (4) non-specific hepatitis and (5) from a patient with congenital porphyria. RNA was studied by the ribonuclease-hydrolysis-basophilic staining technic, and APh by a modified Gomori method. Formaldehyde-containing fixatives are satisfactory for subsequently demonstrating RNA by ribonuclease hydrolysis. Routine acid formalin fixation may produce excessively basophilic staining. Zenker's fluid may produce hypobasophilia. Uniform results are attained by decreasing or increasing staining time. Acetone fixation (as for APh) is unsatisfactory for subsequent enzymatic hydrolyses. On the basis of reduction of basophilia by ribonuclease hydrolysis, gallocyanine-chromalum staining for sixty hours at pH 2.5 is more specific for hepatic RNA than toluidine blue staining. Cirrhotic areas contained numerous reticular fibers, but no elastic fibers, were strongly periodic acid-Schiff's reagent (PA-S) positive and were slightly metachromatic. PA-S staining was reduced by trypsin hydrolysis. PA-S staining and metachromasia were not reduced by hyaluronidase or salivary amylases, indicating absence of hyaluronic acid and glycogen in these reactions.

EFFECT OF ANTIBIOTICS ON FECAL PIGMENTS. DEXTROROTATORY UROBILIN, ITS PROPERTIES AND SIGNIFICANCE. *G. Watson James, M.D., Anne Anderson, B.S. (by invitation) and Vivian Wilkerson, B.S. (by invitation).* (From the Laboratories for Clinical Investigation, Department of Medicine, Medical College of Virginia, Richmond, Va.)

Stercobilin, strongly levorotatory, isolated from feces by Watson, and urobilin IX, *a*, optically inactive, prepared from mesobilirubinogen synthetically, have both been thoroughly described. A dextrorotatory urobilin from infected bile, and in feces of one patient following oral aureomycin has been reported but not isolated in quantities for adequate study.

From patients with various hemolytic anemias, stercobilin was isolated. Then aureomycin or terramycin was given for several days. When the Ehrlich reaction had returned a crystalline dextrorotatory urobilin was regularly obtained from the feces in large quantities. In one patient with N^{15} labelled red cells, the isotope content of stercobilin and *d*-urobilin was the same, indicating a common source. *d*-Urobilin was present in the feces for as long as two months after the antibiotics had been discontinued. During chloromycetin administration only stercobilin was obtained.

d-Urobilin possesses some of the chemical and physical properties of both urobilin IX, *a* and stercobilin. Two crystal forms have been observed. The chemical reactions are more similar to those of urobilin IX, *a*. The Ehrlich reaction, both quantitatively and qualitatively, is identical with stercobilinogen, and *d*-urobilinogen

after the Terwen procedure is quantitatively extractable with petroleum ether. Other properties, its significance and possible modes of origin will be discussed.

USEFULNESS OF SERUM CHOLINESTERASE DETERMINATION IN LIVER DISEASE AND MALIGNANCY: A PRELIMINARY REPORT. *David W. Molander, M.S., M.D. (by invitation), Max Freedman, Ph.D. (by invitation) and John S. LaDue, M.D., Ph.D.* (From the Pack Medical Group, New York, N. Y.)

Serum cholinesterase activity was determined in 120 normal controls and in 100 patients by a colorimetric method that compares favorably with Michel's potentiometric method. In addition, several other standard liver function tests were determined. Low levels were found in patients with acute parenchymal liver disease. The levels varied in cirrhotics. In patients with widespread metastatic carcinoma with metastases to the liver, low levels were general. In cases of lymphoma with liver involvement, low levels were consistent. In general, lower levels were observed in patients with more extensive disease than in those with less involvement. In patients with lymphoma levels progressed toward normal with treatment and clinical improvement.

In some cases in which the other liver function tests were not greatly altered the serum cholinesterase was low and was a useful guide to the clinician in planning the management of these patients. It was helpful in interpreting the values of other liver function tests particularly in patients with parenchymal liver disease and intrahepatic biliary obstruction in which elevated alkaline phosphatase levels may falsely lead to surgical intervention.

The distinct clinical impression was gained that serum cholinesterase activity is a further useful liver function test in detecting liver disease, in following improvement in cases of lymphoma with liver involvement, in evaluating patients with possible liver metastases and finally in differentiating the etiology of jaundice in various patients.

HYPOKALEMIA IN PORTAL CIRRHOSIS: FREQUENCY AND THERAPEUTIC SIGNIFICANCE. *E. L. Artman, M.D. (by invitation) and Robert A. Wise, M.D.* (From the Department of Medicine, Baylor University College of Medicine and the Veterans Administration Hospital, Houston, Tex.)

In July, 1950, hypokalemia was noted in a severely ill, comatose patient with portal cirrhosis. Hypokalemia was noted in hepatocellular disease by Snell in 1941, and recently by Latner, and Farber et al. Latner emphasized that potassium should be given to prevent further depression from glucose administration.

Thirty patients were studied to ascertain its frequency and therapeutic significance. Serial studies of serum potassium and sodium, total base, liver function and electrocardiograms were obtained. The clinical diagnoses were confirmed in eight by needle biopsy, in eight by necropsy and in one at laparotomy. Hypopotassemia was noted in twenty-five of thirty patients; serum potassium was normal in five. In eight the hypokalemia persisted despite adequate diet and additional potassium administration. In ten cases of coma potassium replacement therapy was instituted. Our studies indicate that hypokalemia may be present in cirrhosis of the liver before therapy and may persist after intravenous administration of glucose is discontinued. The hypokalemia is greater and more prolonged in the more severe cases. Replacement potassium therapy in addition to conventional measures resulted in recovery of eight of our ten cases of hepatic coma. Such results indicate that corrections of hypokalemia may be of critical therapeutic significance.

Case Report

A Hemorrhagic State during Pregnancy*

With the Presence of Maternal Rh Antibodies, Death of the Fetus and Hypofibrinogenemia

OSCAR D. RATNOFF, M.D., CARL F. LAUSTER, M.D., JOHN G. SHOLL, M.D.
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HEMORRHAGE is among the leading causes of maternal death in the United States. During the last few years it has become evident that certain instances of hemorrhage during pregnancy have been associated with disturbances in the blood-clotting mechanism. In 1950 Weiner, Reid, Roby and Diamond described three pregnant women who exhibited severe hemorrhagic phenomena at the time of delivery.[1] In each case the patient's blood was Rh negative and contained appreciable quantities of antibodies against the Rh factor. The fetuses appeared to have died *in utero* from eight to ten weeks before delivery. No abnormalities in the clotting mechanism had been demonstrated until the onset of labor. In each case the bleeding during labor was associated with the presence of extreme hypofibrinogenemia, and the blood-clotting mechanism returned to normal shortly after delivery. No satisfactory explanation for the hypofibrinogenemia could be found but the observations which Weiner and his associates reported made it seem unlikely that the patients had hepatic damage or that their blood possessed unusual fibrinogenolytic or fibrinolytic activity.

Recently at University Hospitals of Cleveland a patient was observed in whom death of the fetus occurred during the sixth calendar month of her pregnancy. The patient's blood was Rh negative and contained Rh antibodies. During the eighth month of her pregnancy various hemorrhagic phenomena occurred which proved to be related to hypofibrinogenemia. Unlike the patients previously described, however, this patient did not go into labor spontaneously. Ten weeks after the first episode of bleeding the patient's uterus and its contents were removed. Immediately thereafter the concentration of fibrinogen in the patient's plasma rose to normal levels and no further hemorrhagic episodes were observed.

CASE REPORT

Mrs. S. (U.H. No. 617-224), a thirty-five year old American-born pregnant housewife of Italian extraction, was admitted to the University Hospitals on September 27, 1951, because of purpura which had been present for one day. The patient's red blood cells were Rh negative and her husband's were Rh positive. She had had three previous pregnancies, in 1946, 1947 and 1949, each of which had resulted in the birth of a healthy, Rh positive child. At the second delivery the placenta was completely adherent and was removed manually. The uterus remained atonic and a postpartum hemorrhage of approximately 800 ml. of blood followed. The patient was given a transfusion of 500 ml. of whole blood which was Rh positive because of an error in blood typing. The third pregnancy was again complicated by a completely adherent placenta which was removed manually without undue bleeding. She was asymptomatic after the last pregnancy.

The patient's last menstrual period began on January 17, 1951, and the expected date of confinement was October 24th. She gained

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about 18 pounds until July. The prenatal course was uneventful until July 31st when the patient became aware of the absence of fetal movements. Aside from a gradual loss in weight of about 8 pounds, she was otherwise asymptomatic. On September 12th, during the eighth calendar month of her pregnancy, the patient awoke one morning with her mouth full of blood. On September 26th, two weeks later, ecchymoses appeared on her legs and arms, and the ankles were swollen, discolored and painful; the patient was admitted to the hospital for study. During the week before her hospitalization the patient had had several epistaxes. Previous to her present illness the patient had no history of hemorrhagic phenomena and her family history was free of hematologic disorders.

At the time of her admission to the hospital the patient did not appear to be ill. Ecchymoses were present on the ankles, shins, knees, hips, wrists and elbows. The right arm and forearm were swollen and ecchymotic, and the ankle and dorsum of the right foot were swollen. The size of the uterus was consistent with a pregnancy of six months' duration, and the fetal heart was not audible.

The patient's red blood cell count was 4,300,000 per mm.^{3}, the hemoglobin was 13.9 gm. per 100 ml. (Sahli), and the hematocrit was 39 per cent. There were 9,600 white blood cells per mm.^{3} of which 74 per cent were segmented neutrophils, 6 per cent non-segmented neutrophils, 15 per cent lymphocytes, 3 per cent monocytes and 2 per cent basophils. There were 382,000 platelets, clot retraction was complete within a few hours, the bleeding time was two minutes and forty-five seconds, the prothrombin time was 72 per cent of normal, and the clotting time was seventeen minutes—all normal values. A tourniquet test was normal. The concentration of ascorbic acid in plasma was 8 μg. per ml., also a normal value. The serum albumin was 5.0 gm. per cent, the globulin, 2.5 gm. per cent and the non-protein nitrogen, 26 mg. per 100 ml. The cephalin-cholesterol flocculation test was negative, the thymol turbidity was 3.0 Maclagan units, and the icterus index was 5. A serologic test for syphilis was negative. An x-ray examination of the abdomen on September 21, 1951, demonstrated a fetus the size of which was consistent with a pregnancy of five or six months' duration.

Repeated determinations were made of the anti-Rh titer of the patient's serum. At no time was more than a trace of Rh antibody demonstrable when the cells were suspended in a solution of 0.85 per cent sodium chloride. When a 30 per cent solution of bovine albumin was used as the medium, Rh antibodies were demonstrable in a dilution of 1:16 on July 30th, August 31st and October 7th, 1:32 on October 30th and November 7th, and 1:64 on November 15th and December 4th. Similar titers were demonstrable on these days when the patient's plasma was mixed with trypsin-treated red blood cells. The indirect Coombs test was positive in each of the sera tested.

The patient was placed at bed rest and on this regimen the ecchymoses and joint swelling gradually disappeared. The patient had several nose bleeds during the first few days of hospitalization. She noted bleeding of the gums whenever she brushed her teeth. At no time were there any signs of impending labor. Vaginal examination about two weeks after the expected date of confinement showed that the presenting part of the fetus was still floating and that the cervix was long and closed. On November 7, 1951, a supracervical hysterectomy was performed under the conditions to be described. The uterus contained a macerated male fetus, 30 cm. in length, within an intact ova sac. The placenta was implanted on the posterior wall of the uterus and extended downward to the region of the internal os. The fetal surface of the placenta was irregular and glistening. In several portions it was a pale yellowish gray; in others, particularly around the circumference, it was dark blue. On section the placenta was firmly adherent to the posterior uterine wall. Near the uterine surface it was dull, yellowish gray while the remaining portion was soft and dark red. Near the external border the placenta was separated from the uterus, leaving a free maternal margin of placenta which varied from 2.2 to 8.3 cm. in different places. Histologically, the venous sinuses of the endometrium and myometrium were engorged and an occasional organized thrombus was observed. The placenta was widely necrosed, a process which appeared to have been present for some time; in some of the necrosed areas there were deposits of calcium. In the necrosed areas patchy zones of antemortem anemic infarcts were seen, along with the deposition of considerable amounts of fibrinoid material between the villi. The pathologic diagnoses were placenta accreta, focal necrosis and calcification of the

placenta, necrosis of the fetal parts and umbilical cord, and focal coagulation necrosis of a hypertrophic myometrium.

The postoperative course was uneventful; no hemorrhagic phenomena were observed and the patient was discharged from the hospital on November 17, 1951. She has since been asymptomatic.

METHODS

Blood specimens for study were drawn from the patient's antecubital veins, usually through a No. 18 gauge needle. A portion of each specimen was used for the determination of the clotting time and the clot lysis time of whole blood. Another portion was decalcified by the addition of one part of 0.1 M sodium oxalate solution to 9 parts of whole blood. The oxalated plasma was separated by centrifugation and used in all determinations requiring oxalated plasma except the determination of fibrinogen. A third portion was mixed with dry oxalate salts in a proportion of 5 ml. of whole blood to 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate; this blood was centrifuged. The oxalated plasma thus obtained was used for almost all the determinations of plasma fibrinogen; in a few cases plasma, decalcified with sodium oxalate, was used instead, and correction was made for dilution by the anticoagulant solution. In certain experiments platelet-deficient native plasma was prepared by high speed centrifugation in the cold, using glassware which had been treated with silicone and needles coated with Arquad.*[2,3] Nearly all the specimens studied were obtained shortly after the patient had breakfasted.

Determination of Clotting Time. One ml. of whole blood was transferred immediately to each of three dry pyrex test tubes with an internal diameter of 11 mm. The tubes were stoppered and incubated. With the exceptions noted, the clotting time was measured at room temperature. Starting five minutes after the blood was drawn, the first tube was examined for evidence of clotting by tilting the tubes approximately once a minute. When the blood in the first tube had clotted, the second tube was examined in the same manner, and, in turn, the third. In the tables only the clotting time of the third tube has been recorded.

* Arquad was obtained through the courtesy of Armour and Co., Chicago.

Determination of Clot Lysis Time. The specimens of blood used for the determination of the clotting time were incubated at 37°c. for a period of one week and examined periodically for evidences of liquefaction of the clots.

Determination of Prothrombin Time. The prothrombin time was determined in duplicate at 37°c. by the addition of 0.1 ml. of the patient's oxalated plasma to 0.2 ml. of a mixture of equal parts of thromboplastin and 0.025 M calcium chloride in pyrex tubes with an internal diameter of 8 mm.

Determination of Fibrinogen Content of Plasma. In duplicate, samples of oxalated plasma were diluted to 10 ml. with 0.85 per cent sodium chloride solution and then clotted in the presence of crushed glass by the addition of 50 National Institutes of Health (N.I.H.) units of bovine thrombin. The mixture was swirled as clotting occurred so that the fibrin which was formed adhered to the glass. The fibrin was then separated from the supernatant plasma by centrifugation and washed twice with sodium chloride solution. The amount of fibrin was then determined by measuring its "tyrosine-like" activity.[4] With this technic the amount of fibrinogen in the plasma in normal non-pregnant women was, on the average, 294 mg. per 100 ml. with a standard deviation of 60.3 and a standard error of 16.1.

In two experiments the concentration of fibrinogen was also determined by measuring the "tyrosine-like" activity of the fraction of plasma precipitated by quarter-saturation with ammonium sulfate. A 1 ml. aliquot of oxalated plasma was diluted with 2 ml. of 0.85 per cent sodium chloride solution, and mixed at room temperature with 1 ml. of neutralized ammonium sulfate solution, saturated at 4°c. After ten minutes the precipitate which formed was separated by centrifugation and the supernatant fluid was discarded. The precipitate was washed twice with 25 per cent saturated ammonium sulfate and each time the supernatant fluid was discarded after centrifugation. The "tyrosine-like" activity of the precipitate was then measured.[4]

Preparation of Fibrinogen Test Solution. Desiccated bovine fibrinogen* was dissolved in barbital buffer. The buffer consisted of 0.125 M sodium chloride and 0.025 M barbital at pH 7.5. The desiccated fibrinogen contained

* Bovine fibrinogen was obtained through the courtesy of Dr. Walter Seegers.

0.9 gm. of sodium chloride for each 3.3 gm. of protein. A small residue remained undissolved, and was separated from the solution of fibrinogen by filtration through No. 1 Whatman filter paper. For this reason in each experiment the actual concentration of fibrinogen in solution was somewhat less than the calculated concentration.

Determination of Fibrinolytic Activity of Plasma. Oxalated plasma was diluted serially with barbital buffer. Three-tenths ml. of diluted plasma were added to 0.3 ml. of a solution of bovine fibrinogen in pyrex tubes with an internal diameter of 8 mm. The concentration of bovine fibrinogen was approximately 250 mg. per 100 ml. This mixture was then clotted with 0.1 ml. of a solution of bovine thrombin containing 10 N.I.H. units per ml. The tubes were stoppered, incubated at 37°C. and observed for evidences of fibrinolysis for four days.

Determination of Inhibitory Activity of Plasma against Plasma Proteolytic Enzyme. The inhibitory activity of plasma against the plasma proteolytic enzyme was determined by measuring its effect on purified bovine enzyme.* The bovine enzyme was first standardized in the following manner: The enzyme was dissolved in buffer and serially diluted with buffer. Three-tenths ml. of each dilution were pipetted into pyrex tubes with an internal diameter of 8 mm. Three-tenths ml. of buffer and 0.1 ml. of a solution of thrombin containing 10 N.I.H. units per ml. were then added to each tube. The tubes were placed in an ice bath and 0.2 ml. of fibrinogen solution were added. The maximal possible concentration of fibrinogen in this solution was 250 mg. per 100 ml. The mixture of enzyme, fibrinogen and thrombin was then transferred to a water bath at 37°C. and the clots which formed were observed for lysis. The fibrinolytic activity of the solutions of bovine plasma proteolytic enzyme differed somewhat from experiment to experiment; the concentration of enzyme which completely lysed the standard fibrin clot in ten minutes varied from about 1.5 to 4 units per ml.

The patient's oxalated plasma was diluted serially with buffer. Three-tenths ml. of each dilution of plasma were mixed with 0.3 ml. of a solution of bovine plasma proteolytic enzyme containing 2.5 units per ml. The mixtures were then incubated at 37°C. for ten minutes. The enzyme-plasma mixtures were then placed in ice bath, and 0.3 ml. of fibrinogen and 0.1 ml. of thrombin solution were added in succession. The tubes were then transferred to a water bath at 37°C. and the clots which formed were observed for the appearance of fibrinolysis. The interval until clot lysis occurred was measured from the time the mixtures were transferred to the water bath.

Determination of the Anticoagulant Activity of Plasma. The anticoagulant activity of plasma was determined by measuring its clot-retarding effect on normal whole blood, using the method described by Conley, Hartmann and Morse.[5]

Determination of Thrombin-Inhibitory Activity of Plasma. Bovine thrombin was diluted serially with barbital buffer. The clotting time of a mixture of 0.1 ml. of the patient's plasma, 0.1 ml. of prothrombin-deficient plasma and 0.1 ml. of thrombin was determined at 37°C. in pyrex tubes with an internal diameter of 8 mm. The prothrombin-deficient plasma was prepared by incubating normal oxalated plasma for ten minutes at 37°C. with one-fifth its volume of powdered barium sulfate, and then removing the barium sulfate by centrifugation.

Preparation of Human Fibrinogen for Intravenous Injection. Human fibrinogen, prepared by the American Red Cross, was obtained through the kindness of Dr. Louis K. Diamond. The fibrinogen was packaged in bottles said to contain, on the average, about 1.7 gm. of clottable protein per 100 ml. Under sterile conditions the contents of each bottle were dissolved in 400 ml. of a 5 per cent solution of glucose in distilled water and the solution was filtered through several layers of gauze before use. The amount of fibrinogen was determined in three of four bottles used and was 1.3, 1.4 and 2.0 gm., respectively.

OBSERVATIONS

The Nature of the Clotting Defect. On October 6, 1952, about three and one-half weeks after the patient had first noted bleeding from the mouth, the clotting time of venous blood at 37°C. was twenty-seven minutes, a normal value. The clots did not appear to be unusual when they first formed. The tubes of clotted blood were incubated at 37°C. About an hour after clotting had occurred the contents of each tube appeared to be fluid except for a small retracted clot about 3 mm. in diameter.

Investigation revealed that the size of this clot was the result of hypofibrinogenemia. The

* Bovine fibrinolysin (plasma proteolytic enzyme) was obtained through the courtesy of Parke, Davis and Company, Detroit, Mich.

concentration of fibrinogen in the patient's plasma was determined by measuring the amount of fibrin which formed when bovine thrombin was added. Using this method there were 91 mg. of fibrinogen per 100 ml. of plasma, or about one-third that of the normal non-

TABLE I
EFFECT OF PATIENT'S NATIVE PLASMA ON THE CLOTTING TIME OF NORMAL BLOOD *

0.1 ml. Buffer (min.)	0.5 ml. Buffer (min.)	0.1 ml. Patient's Plasma (min.)	0.2 ml. Patient's Plasma (min.)	0.5 ml. Patient's Plasma (min.)
11	8	11	6	8
14	11	11	11	8
14	14	12	12	8

* Clotting time at 37°C. of 1 ml. portions of normal blood to which was added buffer or the patient's plasma in the amounts indicated; triplicate determinations.

pregnant woman. The question then arose whether only a small amount of fibrin was formed because the conversion of fibrinogen to fibrin was impaired. To study this possibility the patient's platelet-deficient plasma was mixed with normal whole blood. The clotting time of this mixture was not significantly different from that of the normal whole blood alone, and the clots which resulted were normal in appearance and retracted normally. In this experiment a circulating anticoagulant which might have inhibited the clotting of normal blood could not be demonstrated in the patient's plasma (Table I); nor could we demonstrate that the patient's plasma possessed excessive thrombin-inhibitory activity which might have interfered with the determination of fibrinogen by the method described. (Table II.) For these reasons it was unlikely that the poor clot formation was due to impairment of the conversion of fibrinogen to fibrin.

From these observations it seemed evident that the small size of the patient's clot could be ascribed to a decrease in the concentration of fibrinogen in the circulating plasma. This assumption was confirmed by determining the amount of protein which was in the fraction of plasma precipitated by quarter-saturation with ammonium sulfate. This fraction consists largely of fibrinogen although other proteins may be present as well. In one such experiment the concentration of fibrinogen in the patient's plasma was 110 mg. per 100 ml. when determined as fibrin, and 138 mg. per 100 ml. by the ammonium sulfate method. Furthermore, repeated electrophoretic analyses of the patient's plasma confirmed the presence of hypofibrinogenemia.

TABLE II
EFFECT OF THROMBIN ON THE CLOTTING TIME OF A MIXTURE OF OXALATED PLASMA AND PROTHROMBIN-DEFICIENT PLASMA *

Initial Concentration of Thrombin (units/ml.)	Clotting Time	
	Patient's Plasma (sec.)	Control Plasma (sec.)
10	11	13
5	17	18
2.5	26	32
1.25	55	62

* Clotting time of a mixture of 0.1 ml. of oxalated plasma, 0.1 ml. of barium sulfate-absorbed plasma (as a source of fibrinogen) and 0.1 ml. of a solution of bovine thrombin, serially diluted with buffer.

(Fig. 1, Table III.) On November 7th the ϕ component of the patient's plasma was present in a concentration of approximately 200 mg. per 100 ml. This component consists largely of fibrinogen, but includes other protein as well.[6] The concentration of the ϕ component after this plasma was defibrinated with thrombin was approximately 120 mg. per 100 ml. From these data it appears that electrophoretically the concentration of fibrinogen in the patient's plasma was about 80 mg. per 100 ml. The significance of the presence of a portion of ϕ component in the patient's defibrinated plasma is not known. However, approximately the same amount of ϕ component remained in a normal plasma defibrinated with thrombin.

Several studies were performed to determine whether the basic pathologic process in this patient was impaired synthesis of fibrinogen or excessive removal of this protein from the blood stream. The patient was given an intravenous infusion of approximately 1.05 gm. of human fibrinogen dissolved in 300 ml. of a solution of 5 per cent glucose in water. The fibrinogen was injected over a period of thirty minutes. The concentration of fibrinogen in the patient's plasma was measured before the infusion, immediately after the completion of the infusion

and one and five hours thereafter. (Table v.) The fibrinogen which had been injected disappeared within five hours. Control experiments could not be performed either in normal subjects or in this patient after hysterectomy. Pinniger and Prunty[7] gave a transfusion of 300 ml. of plasma containing 1.36 gm. of fibrinogen to a young girl who had congenital afibrinogenemia. Twenty-four hours later the concentration of fibrinogen in the plasma of Pinniger and Prunty's patient was 78 mg. per 100 ml. and significant amounts of fibrinogen were still present after ninety-six hours. A comparison of these two patients suggests that in the present case the fibrinogen which was injected was removed from the plasma at an excessive rate.

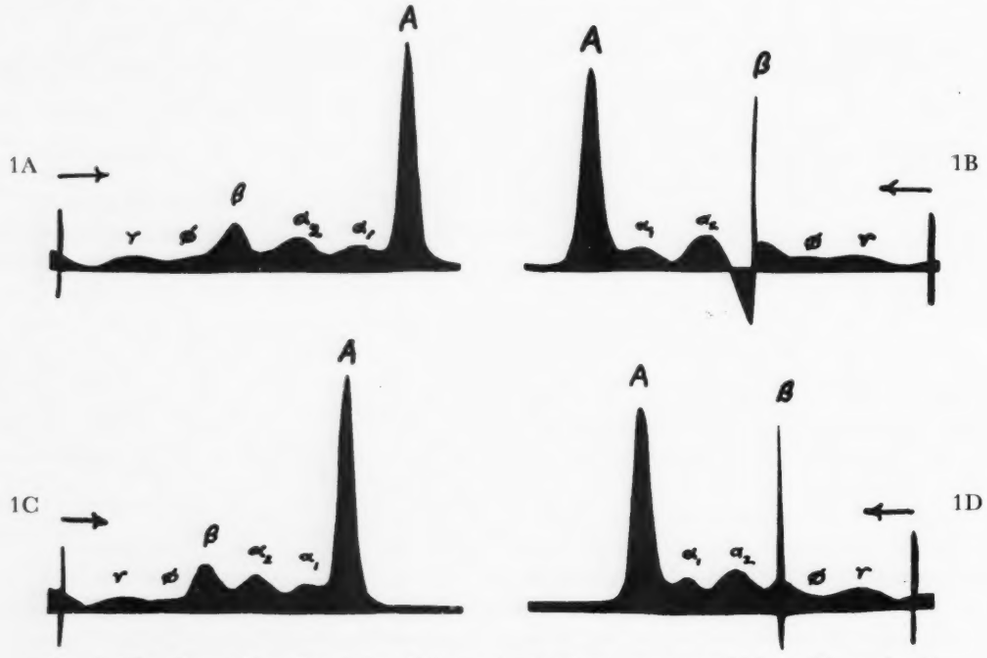

FIG. 1. The electrophoretic pattern of the patient's plasma preoperatively on November 7, 1951. A and B are the ascending and descending films of the patient's oxalated plasma. C and D are the ascending and descending films of the patient's plasma after defibrination with bovine thrombin.

Human plasma contains a proteolytic enzyme system which can digest fibrinogen. Ordinarily, this enzyme system seems to be inactive in the circulating plasma but under unusual circumstances may become active *in vivo*. A few patients have been described in whom severe hemorrhagic phenomena occurred apparently because the plasma fibrinogen had been destroyed by this enzyme.[8–11] In the patient under study clots which formed from whole blood and from platelet-deficient plasma were incubated at 37°C. Within about an hour the clots retracted to an unusually small size. However, these clots did not change in appearance during the next week. In other words, the patient's plasma did not appear to possess unusual fibrinolytic activity. Furthermore, oxalated plasma in final concentrations ranging from 1 part in 23 to 1 part in 1500 did not digest clots formed by the addition of thrombin to bovine fibrinogen. Human plasma also has the property of inhibiting the plasma proteolytic enzyme. The inhibitory activity of the patient's plasma against bovine plasma proteolytic enzyme was not abnormal. (Table IV.) One may conclude from these observations that the hypofibrinogenemia in this patient was not the result of the destruction of fibrinogen by the plasma proteolytic enzyme.

The patient's prothrombin time was slightly prolonged compared with normal plasma. (Table v.) This prolongation of the prothrombin time was not corrected by the addition of bovine fibrinogen or human oxalated plasma from which the prothrombin had been removed, indicating that a moderate deficiency in circulating prothrombin was present.

Observations during the Course of the Patient's Illness. Repeated studies of the patient's clotting mechanism were made during her illness. The

degree of hypofibrinogenemia was remarkably constant and slight hypoprothrombinemia persisted. (Table v, Fig. 2.) The clotting time remained normal. Although the clots always retracted to an excessively small size, at no time was fibrinolytic activity observed nor was it possible to demonstrate any increased fibrinolytic activity when the patient's diluted plasma was incubated with a clot formed from bovine fibrinogen and thrombin.

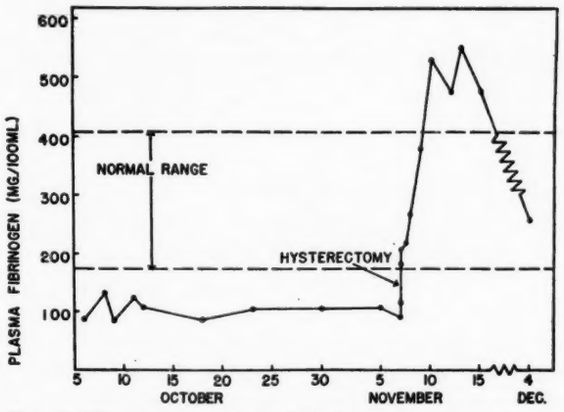

FIG. 2. The concentration of fibrinogen in the patient's plasma during the period of observation.

TABLE III
ELECTROPHORETIC ANALYSIS OF THE PATIENT'S PLASMA*

	Ascending Film (gm./100 ml.)	Descending Film (gm./100 ml.)
A) Plasma		
Albumin	4.11	4.59
$\alpha 1$	0.48	0.58
$\alpha 2$	1.03	0.88
β	1.24	0.87
ϕ	0.22	0.18
γ	0.53	0.49
B) Plasma defibrinated with thrombin		
Albumin	4.10	4.15
$\alpha 1$	0.53	0.60
$\alpha 2$	1.01	1.10
β	1.17	1.13
ϕ	0.12	0.12
γ	0.57	0.41

* November 7, 1951, electrophoresis performed in barbital buffer at pH 8.5, ionic strength 0.1. (Fibrinogen is a part of the ϕ fraction.)

On November 7, 1951, two weeks after the expected date of confinement, a subtotal hysterectomy was performed. The patient was prepared by the intravenous injection of human fibrinogen in order to increase the concentration of this substance to a normal level. The initial incision was made when approximately 600 ml. of solution, containing about 2.5 gm. of fibrinogen, had been infused. Six hundred ml. more of fibrinogen solution were infused during the operation which lasted seventy minutes. During the course of the operation no unusual difficulty with hemostasis was encountered. Just after the uterus was removed a suture ligature constricting one of the branches of the uterine artery loosened but the vessel was clamped and religated without undue blood loss and without any indication that a clotting defect was present. No changes in the fibrinolytic activity of the patient's plasma could be demonstrated during the operation.

TABLE IV
PROTEASE INHIBITORY ACTIVITY OF OXALATED PLASMA*

Initial Concentration of Plasma	Concentration of Plasma Proteolytic Enzyme (units/ml.)	Clot Lysis Time		
		Patient's Plasma (min.)	Control Plasma (min.)	Buffer‡ (min.)
1/10	2.5	†	†	..
1/20	2.5	35	35	..
1/40	2.5	35	35	..
1/80	2.5	16	17	..
1/160	2.5	16	13	..
1/320	2.5	24	16	..
1/640	2.5	24	7	..
0	2.5	..	..	22
0	1.25	..	..	42

* Clot lysis time at 37°C. of a mixture of 0.3 ml. bovine plasma proteolytic enzyme solution, 0.3 ml. oxalated plasma, serially diluted with buffer, 0.1 ml. bovine thrombin solution and 0.3 ml. bovine fibrinogen solution. The enzyme and plasma were incubated at 37°C. for ten minutes before the addition of thrombin and fibrinogen.
† Lysis occurred overnight.
‡ Substituted for plasma.

Immediately postoperatively the concentration of fibrinogen in the patient's plasma was 208 mg. per 100 ml., well within the normal range. About eight hours postoperatively the patient's blood pressure dropped to 90/50 mm. Hg. The patient was given a transfusion of 500 ml. of citrated bank blood and her blood pressure returned to normal within one and one-half hours. Otherwise, her postoperative course was uneventful. During the next few days

the concentration of fibrinogen in the patient's plasma rose to levels somewhat above the normal range.

On the third and fifth postoperative days the clotting time of whole blood was forty-seven and fifty-one minutes, respectively. This prolongation of the clotting time was not accompanied by any hemorrhagic phenomena. The cause of the prolonged clotting time was unexplained. The patient's plasma corrected the clotting defect of hemophilic plasma. In this experiment an equal mixture of the patient's oxalated plasma and hemophilic oxalated plasma clotted within three and one-half minutes upon recalcification; the patient's plasma alone clotted in three minutes, and the hemophilic plasma alone in sixty minutes. On the sixth postoperative day the patient's whole blood clotting time was normal, and it was not possible to demonstrate the presence of a circulating anticoagulant in the patient's platelet-deficient plasma. The patient was discharged from the hospital on the seventh day after her operation. On December 4, 1951, the clotting time, the prothrombin time and the concentration of fibrinogen in the patient's plasma were all normal.

TABLE V

DATA CONCERNING THE BLOOD CLOTTING MECHANISM DURING THE COURSE OF THE PATIENT'S ILLNESS

Date	Clotting Time (min.)	Prothrombin Time		Plasma Fibrinogen (mg./100 ml.)	Remarks
		Patient (sec.)	Control (sec.)		
10/6/51	27	22	18	92	
10/8/51	22	21	19	132	
10/9/51	27	23	20	92	
10/11/51					
10:00 A.M.	30	23	19	125	
10:32 A.M.	20	23	19	170	Specimen at end of infusion of 1.05 gm. fibrinogen in 300 ml. 5% glucose
11:32 A.M.	16	23	19	158	Specimen 1 hour after infusion
3:32 P.M.	13			106	Specimen 5 hours after infusion
10/12/51	28	28	20	108	
10/18/51	24	22	20	89	
10/23/51	16	22	20	111	
10/30/51	16			110	
11/5/51	19	21	19	104	
11/7/51					
2:05 P.M.	29	26	21	91	Preoperative specimen
2:28 P.M.	23	25	21	115	Preoperative specimen after infusion of 400 ml. of fibrinogen solution
3:22 P.M.	15	25	21	186	Specimen 47 minutes after operation begun, 20 minutes after hysterectomy, after infusion of 800 ml. of fibrinogen solution
3:50 P.M.	20			208	Specimen 4 minutes after operation completed, after infusion of 1,200 ml. fibrinogen solution
6:12 P.M.	21	24	21	218	
11/8/51	24	25	20	274	
11/9/51	24	26	20	388	
11/10/51	47	25	18	536	
11/12/51	51	24	19	469	
11/13/51	12	23	20	552	
11/15/51	15	20	20	473	
12/4/51	24	18	19	260	

COMMENTS

Unlike the patients studied by Weiner and his associates[1] the patient described herein did not deliver spontaneously. Her pregnancy was

terminated by performance of a subtotal hysterectomy. Removal of the uterus and fetus was followed by immediate restoration of the blood-clotting mechanism to an apparently normal state.

To explain the hypofibrinogenemia which they observed, Weiner and his associates offered three possible explanations. They believed that one possibility was that the circulating fibrinogen was being removed by excessive plasma proteolytic activity. However, neither in our patient nor in those previously studied was there any indication of abnormal plasma proteolytic activity which might have led to the excessive destruction of fibrinogen *in vivo*.

The second hypothesis of Weiner and his coworkers was that the rate of synthesis of fibrinogen was decreased. They believed that this was unlikely since hepatic function was normal in their patients. It was not possible to determine with certainty if the hypofibrinogenemia in the present case was caused by a decreased rate of synthesis or an increased rate of destruction or utilization of this protein. In a single trial experiment, performed before the patient's hysterectomy, fibrinogen which was injected intravenously disappeared within a few hours. This is unlike the experience of Pinniger and Prunty.[7] In a patient lacking circulating fibrinogen they found appreciable amounts of fibrinogen in the blood stream for at least ninety-six hours after this substance had been injected intravenously. Pinniger and Prunty's data suggest that the hypofibrinogenemia in our patient was due to increased destruction or utilization. However, additional studies are needed.

The third hypothesis proposed by Weiner et al. was that clotting had occurred intravenously. They postulated that the disintegration of the fetal membranes and placenta in this condition might have permitted highly thromboplastic amniotic fluid to enter the blood stream and clot the blood intravascularly. The data presented make this seem to be a reasonable hypothesis. Placental tissue itself is a rich source of thromboplastin[12] and it is possible that material from the diseased placenta could have trickled into the blood stream and defibrinated the plasma. Whether an antigen-antibody reaction between the fetal tissues and maternal serum is important in the pathogenesis of the hypofibrinogenemia is unknown.

Therapy in hypofibrinogenemia must be directed toward restoration of the normal mechanism of blood clotting. Accordingly, our patient was prepared for operation by the intravenous injection of sufficient human fibrinogen to correct the hypofibrinogenemia, a procedure suggested by Weiner. In similar cases a subtotal hysterectomy, performed while the clotting defect is temporarily corrected by the fusion of fibrinogen, would appear to be preferable to the induction of labor. The former procedure provides the surgeon with greater opportunity to control any hemorrhage which might occur. The question also arises whether hysterotomy with removal of the fetus ought not to be performed prophylactically in those instances in which fetal death is recognized in patients with Rh iso-sensitization, prior to the appearance of hemorrhagic phenomena.

SUMMARY

A patient is described in whom hemorrhagic phenomena were associated with hypofibrinogenemia. This patient was Rh negative, had Rh antibodies in the circulating blood and a dead fetus *in utero*. Unlike those patients previously described the hypofibrinogenemia persisted for at least four and a half weeks. The hemorrhagic state was corrected by subtotal hysterectomy which was performed while the plasma level of fibrinogen was sustained by intravenous infusion of this substance.

Acknowledgment: We are indebted to Dr. Austin S. Weisberger for pointing out that the patient's hemorrhagic diathesis was the result of a defect in the mechanism of blood clotting. It is a pleasure to acknowledge the technical assistance of Mrs. Rosemary Ashe, Mrs. Velma Axelrod and Miss Jean Stang. Thanks are also due to Dr. Louis Pillemer for his suggestions and criticism.

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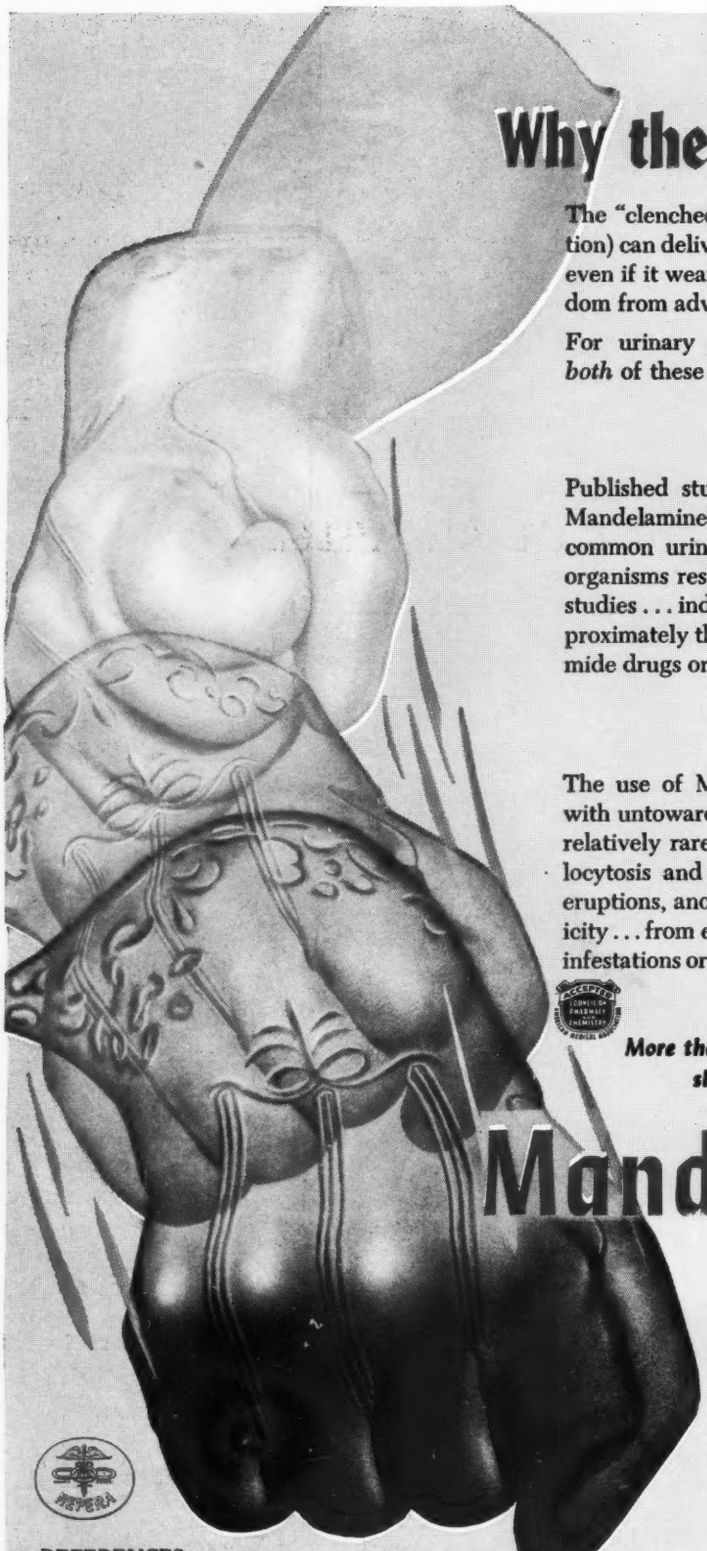

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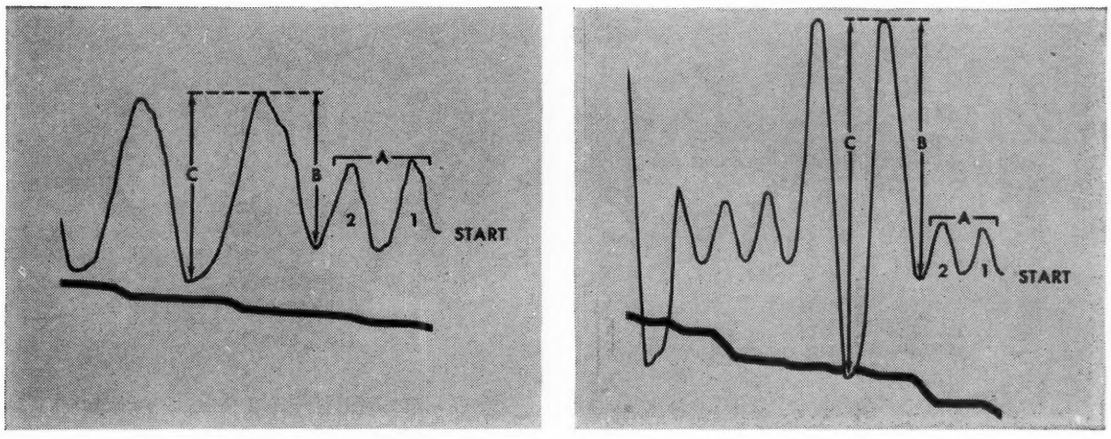

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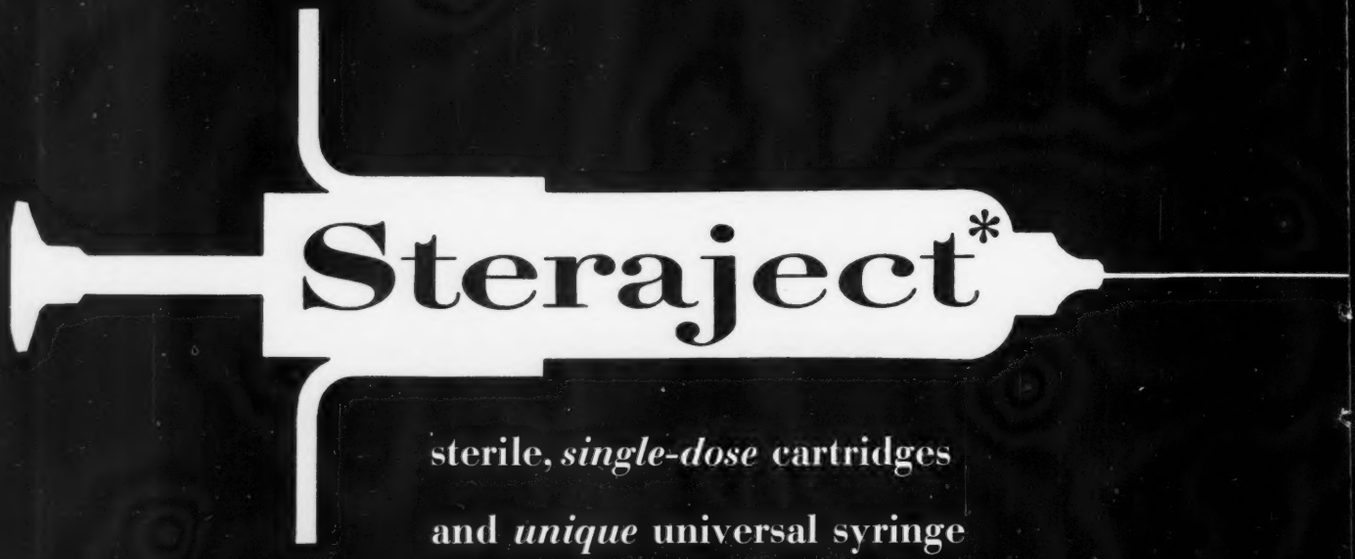

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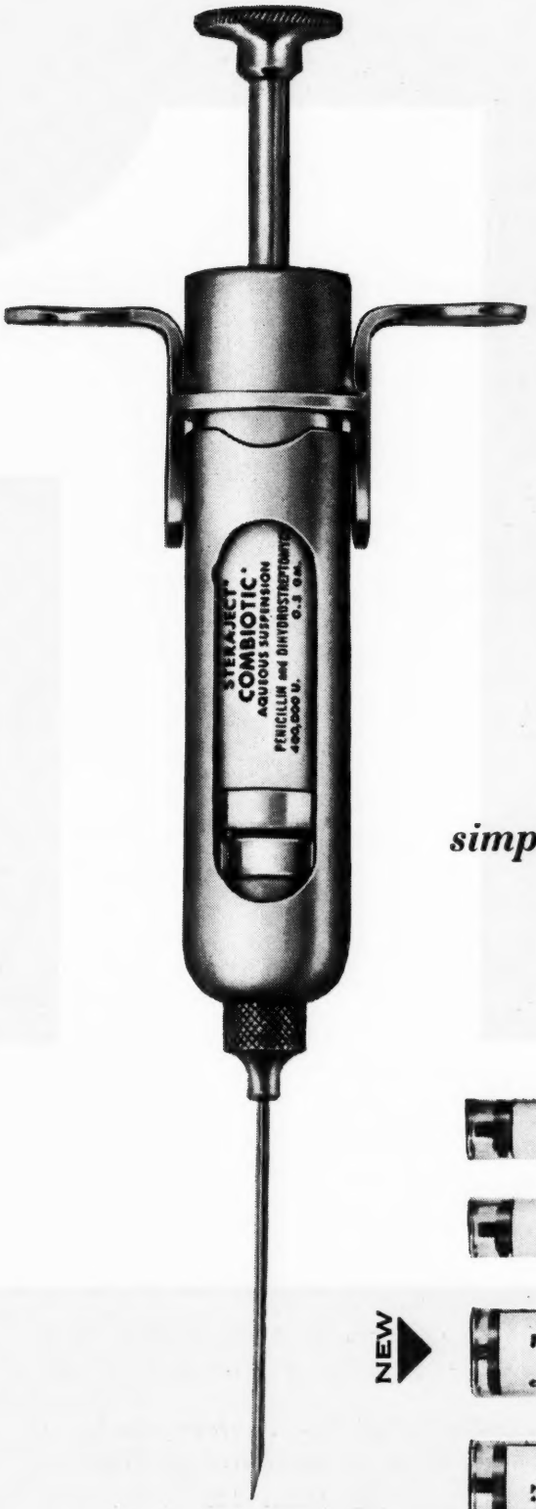

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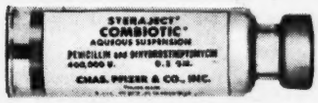

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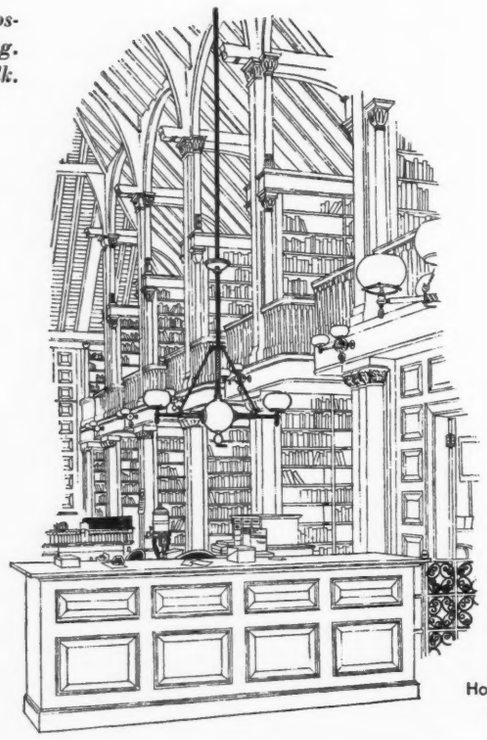

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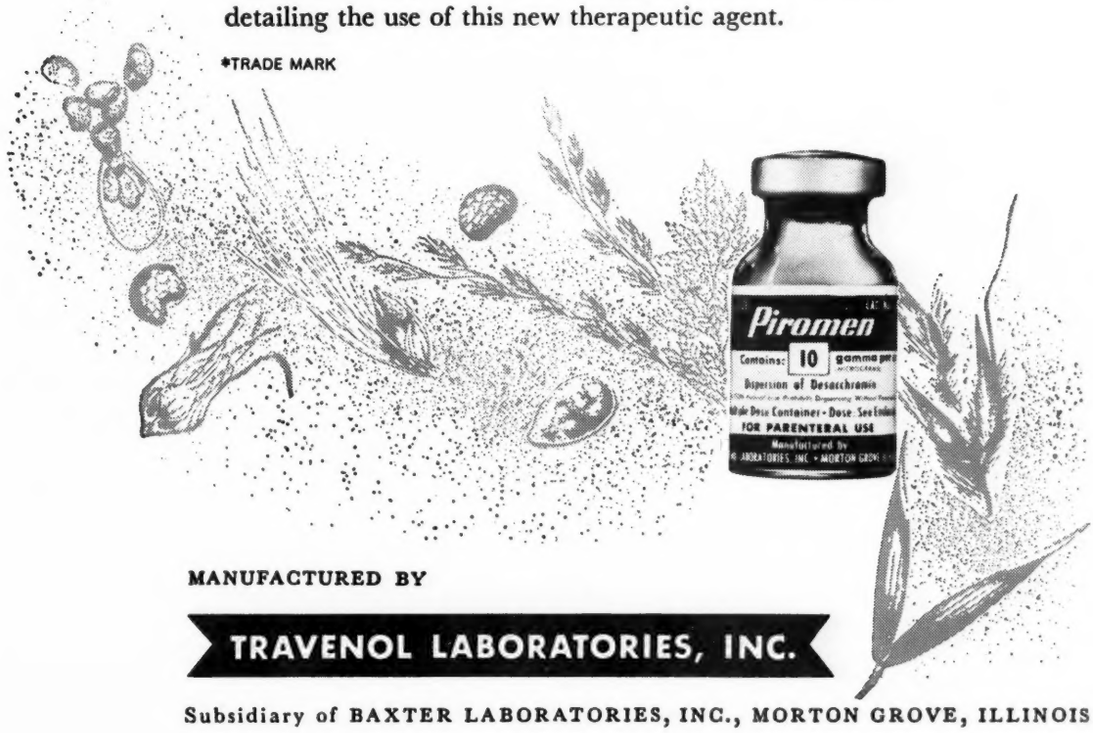

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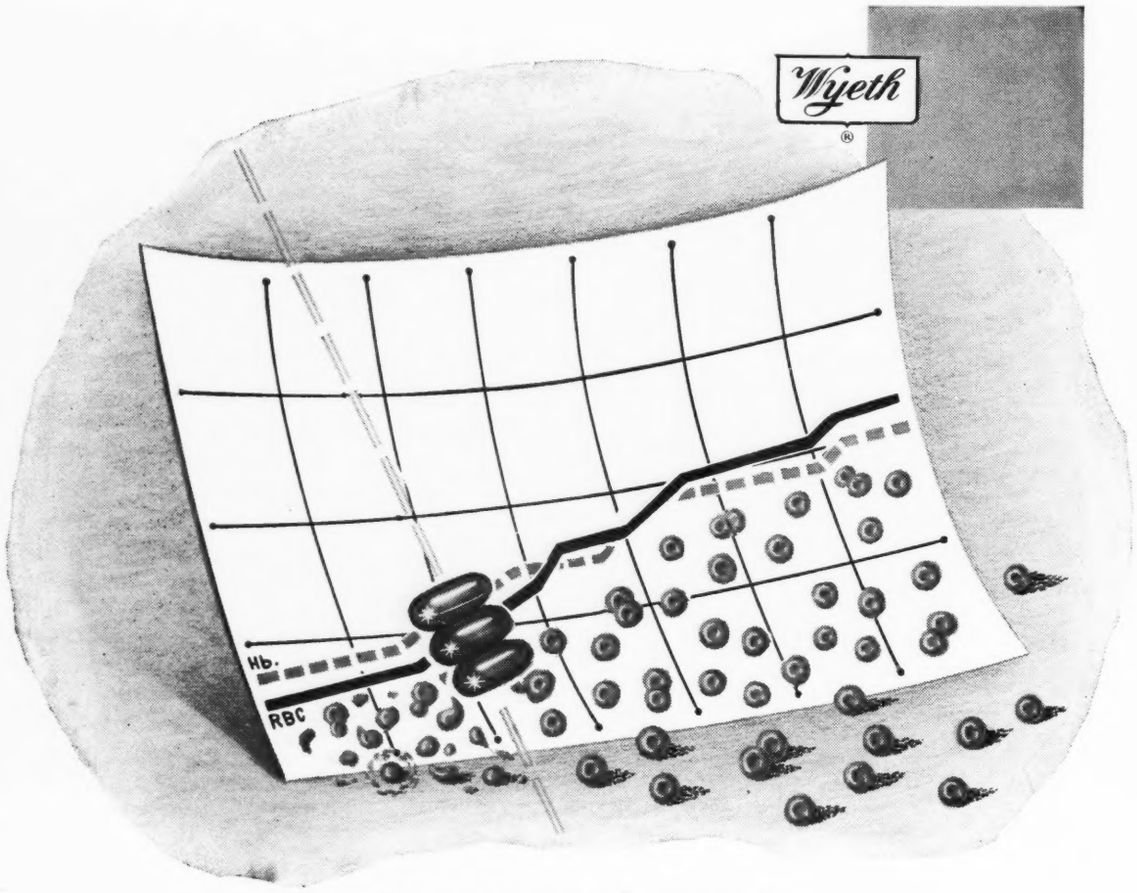

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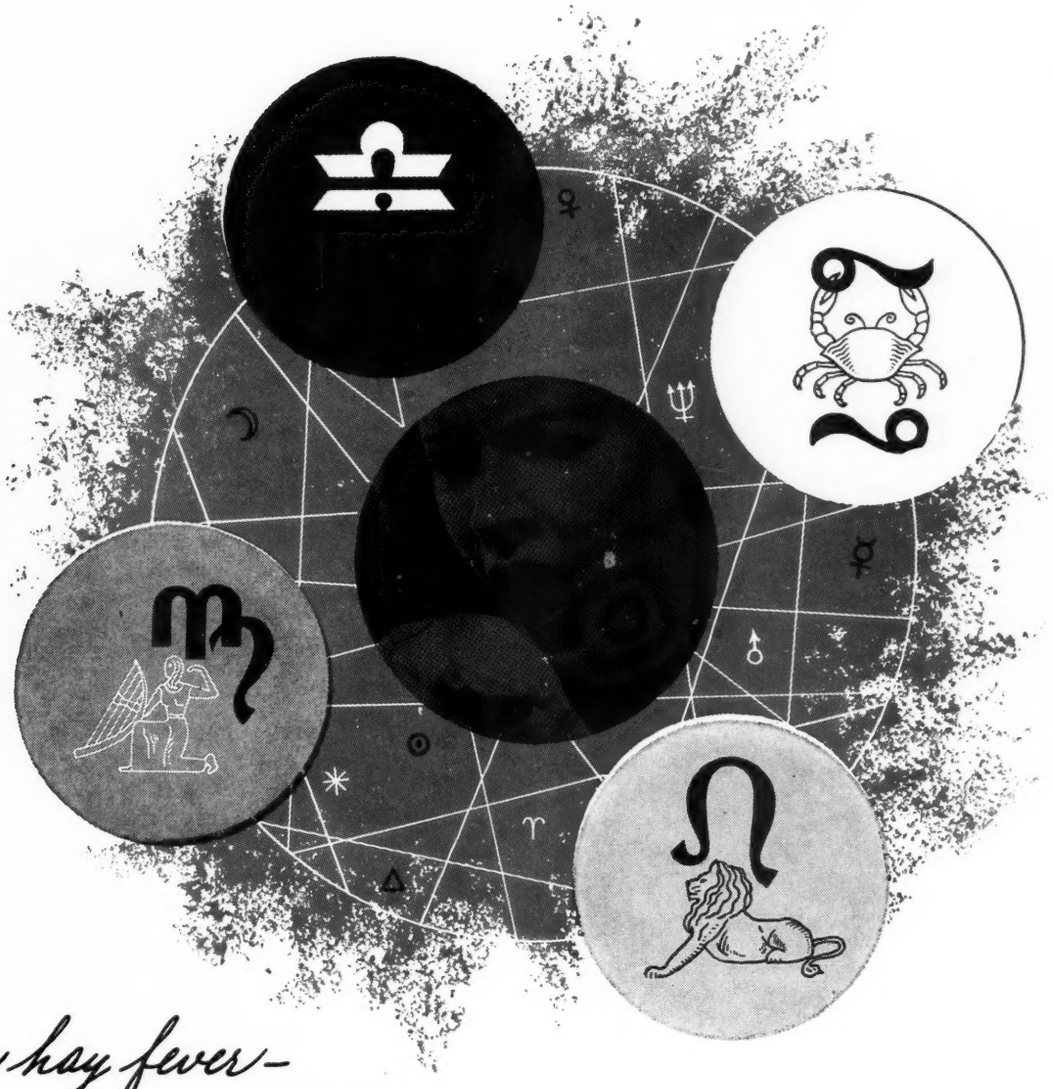

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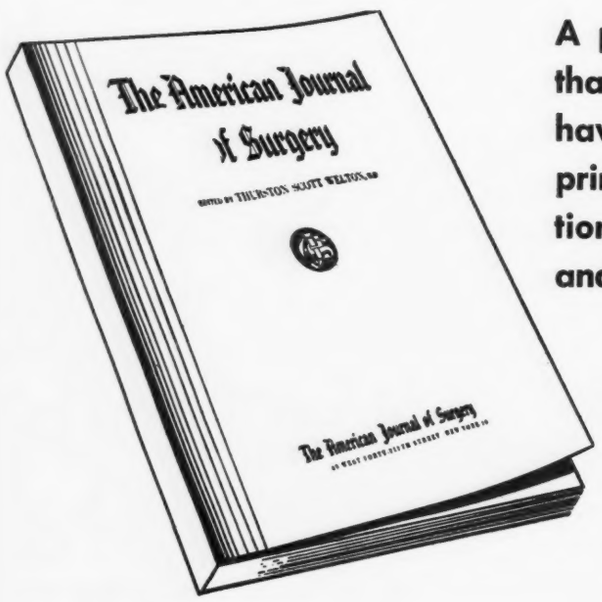

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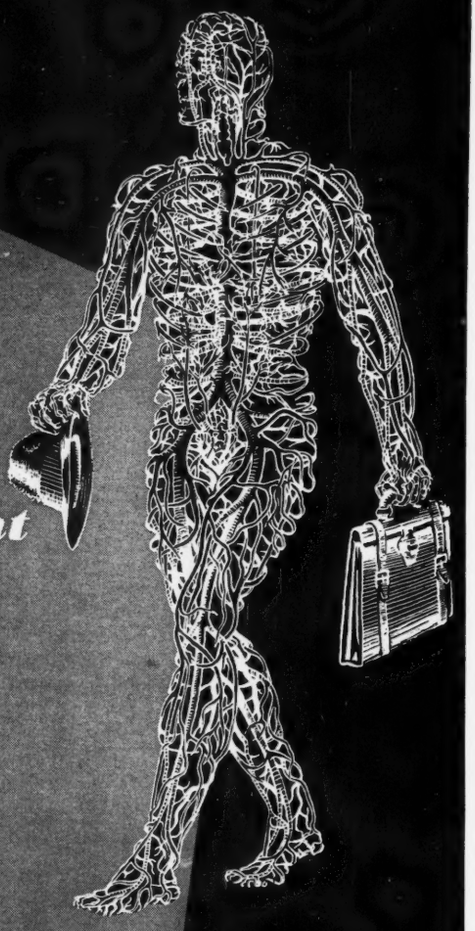

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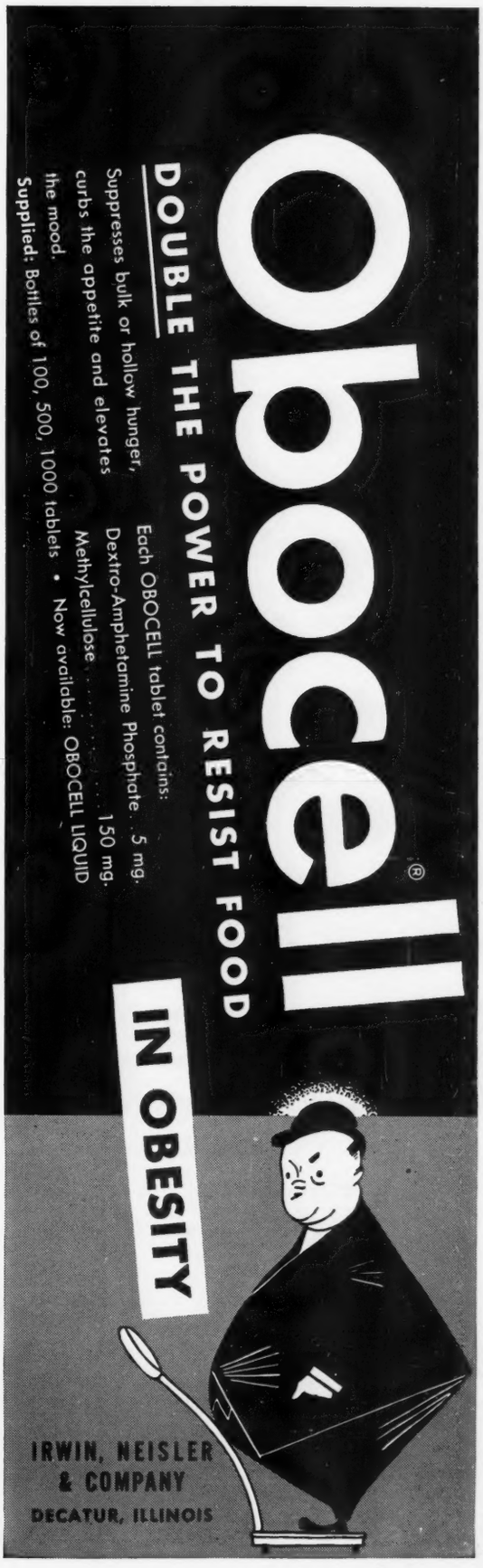
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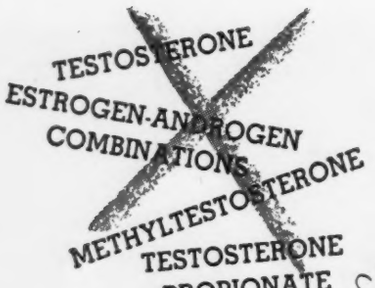

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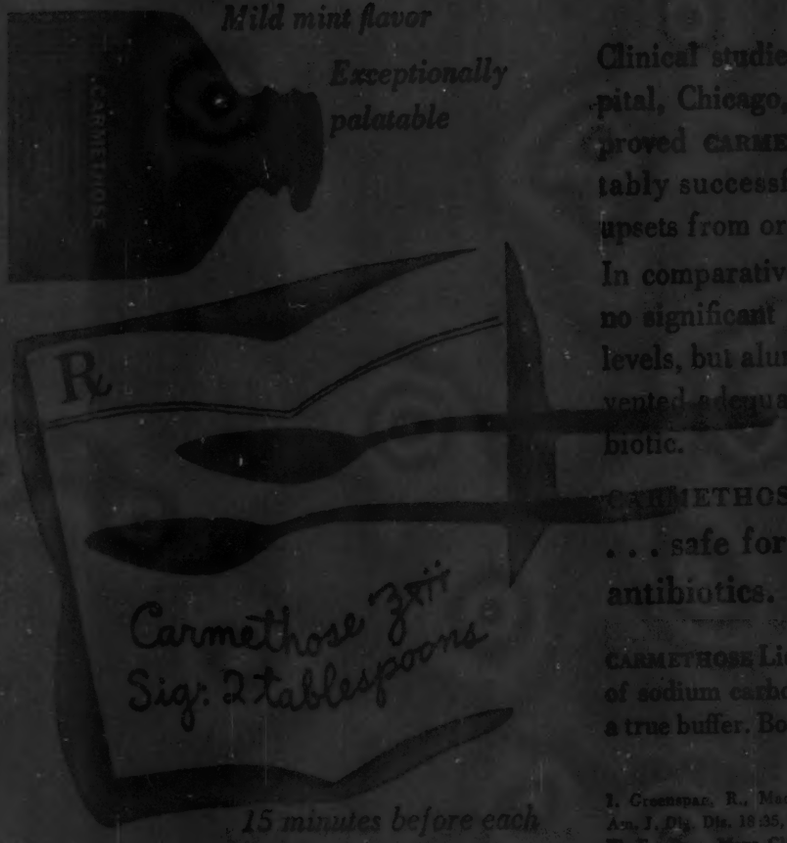

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